Introduction

Membership of the core group
The core group responsible for considering whether recommendations in DPLD are appropriate and for writing a draft document on diagnosis and assessment consisted of: Dr M Cushley, Dr A Davison, Dr R du Bois, Dr C Flower, Dr A Greening, Dr N Ibrahim, Dr I Johnston (Chairman), Dr D Mitchell and Professor A Pickering. Professor J Gibson and Dr J Egan were co-opted onto the group in considering treatment recommendations.

Nomenclature

The parenchyma of the lung includes the pulmonary alveolar epithelium and capillary endothelium and the spaces between these structures, together with the tissues within the septa including the perivascular and perilymphatic tissues. More centrally it includes the peribronchiolar and peribronchial tissues. Many terms have been used to encompass the large group of disorders that primarily affect the lung parenchyma in a diffuse manner. Diffuse parenchymal lung disease (DPLD) is increasingly in favour worldwide as a generic term for these disorders, in preference to terms such as interstitial lung disease or diffuse lung disease. Alveolar filling diseases are also included under DPLD because of the similarity of presentation.

Need for recommendations in the management of DPLD

The DPLDs are important, accounting for about 15% of respiratory practice.[1] They comprise a very wide spectrum of pathologies, presentations, and outcomes. Despite their acknowledged complexity, no consensus on the general management of these disorders is available. There is a serious paucity of evidence about the management of DPLDs, but the morbidity of the DPLDs themselves and the treatments available may be high, with potentially serious consequences therefore for mismanagement. New techniques have become available which may have a role in the management of DLPD, but the place of these techniques has not hitherto been adequately addressed. There is concern that DPLDs may be poorly recognised and managed by non-specialists. Respiratory specialists are the only group with appropriate training and skills to deal with the complexity of the diagnosis and management of these conditions. There is, however, evidence of wide variation in the management of DPLDs amongst respiratory physicians.[2 3]

Against this background the British Thoracic Society (BTS) Standards of Care Committee set up a sub-committee to formulate recommendations on DPLD management.

The target

Part 1 of these recommendations covers the general recognition, investigation, and assessment of a particular group of patients with DPLD—namely, those who usually present with diffuse shadowing on chest radiography and with gradual or subacute onset of symptoms. It is recognised that some patients will have shadowing on the chest radiograph with no or few symptoms, while others will have symptoms due to DPLD but a normal chest radiograph. Such patients are also included in the remit of this document.

In Part 2 the treatment of a range of DPLDs is reviewed, with particular emphasis on cryptogenic fibrosing alveolitis (CFA), sarcoidosis, and referral for transplantation.

Purpose of the recommendations

- To support improved recognition, diagnosis, assessment, and treatment of patients with DPLD.
- To raise awareness of the importance of DPLDs.
- To provide an authoritative current literature review of DPLD management.
- To provide practical, evidence and consensus based recommendations that will aid the development of clinical services for patients with DPLD.

Methods of guideline production

The core group initially defined the target and the purpose of the recommendations. Independent Medline literature searches from 1985 onwards were carried out by the Library of the Royal Society of Medicine (on diagnosis and assessment of DPLD) and by the NHS Library Department of University Hospital Nottingham (on treatment of DPLDs). After additional hand searching of the literature, a draft document was produced containing recommendations based on position papers on (1) clinical assessment, (2) imaging, (3) lung function and exercise testing, (4) the role of bronchoalveolar lavage and DTPA scanning, (5) biopsy and pathology, and (6) DPLD in immunocompromised patients. The entire document was reviewed by a wider group of respiratory physicians, thoracic surgeons, radiologists, pathologists, and general practitioners (listed in Appendix 1). The recommendations were also reviewed by BTS members at a symposium at the BTS Meeting in December 1997. Modifications were then made and an algorithm for the management of DPLD was added.

Following agreement that the final document should also contain recommendations on treatment, the group produced literature reviews on treatment of (1) CFA, (2) sarcoidosis, (3) other DPLDs, and (4) transplantation. The treatment recommendations were then agreed by consensus between the 11 members of the group.

The summary recommendations in Part 1 and the treatment recommendations for CFA, sarcoidosis, other DPLDs, and referral for transplantation in Part 2 were graded according to the criteria of the Scottish Intercollegiate Guidelines Network (grades A to C) which is given in Appendix 2.

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Part 1: Diagnosis and assessment of diffuse parenchymal lung disease

Summary of recommendations

Referral

- Patients with DPLD or suspected DPLD should be under the direct or joint care of a respiratory physician. (C)

Clinical

- An accurate detailed history is vital. There should be particular emphasis on coexisting or past systemic disease, medication, occupational and environmental exposures, travel, family, and smoking history, and the possibility of underlying immunosuppression, including HIV. (C)
- In addition to careful respiratory examination, there should be evaluation of systemic disease including fever, cardiac status, rashes, eye signs, hepatosplenomegaly, arthritis and urine dipstick. (C)
- The initial laboratory investigations should include full blood and eosinophil counts, viscosity or erythrocyte sedimentation rate (ESR), serum urea and electrolytes, creatinine, calcium, liver function tests, and autoantibodies (antinuclear and rheumatoid factors). Depending on the clinical setting, further investigation may need to include additional autoantibodies (antineutrophil cytoplasmic antibody (ANCA), glomerular basement membrane antibody (anti-GBM)), serum precipitins, electrocardiography and echocardiography. (C)
- Previous radiographs or reports should be sought. (C)

Imaging

- Radiologists and respiratory physicians should meet regularly to jointly evaluate imaging in patients with DPLD. (C)
- Where a radiologist's report suggests DPLD on a chest radiograph, it should also raise the question of respiratory physician involvement. A statement such as "suggest referral to respiratory physician" is appropriate. (C)
- In patients for whom a diagnosis is reached with a high degree of certainty from clinical assessment and chest radiography, high resolution computed tomographic (HRCT) scanning is not required, except in cryptogenic fibrosing alveolitis (CFA). (C)
- In patients for whom the diagnosis is uncertain after chest radiography and clinical assessment, HRCT scanning is the next investigation of choice and should precede biopsy. (C)
- HRCT scanning is valuable in detecting DPLD in patients with a normal chest radiograph. (B)
- In the appropriate clinical setting, appearances on the HRCT scan may be sufficiently characteristic to preclude the need for biopsy samples to be taken. (B)
- HRCT scanning also provides prognostic information in CFA and is recommended in this disease irrespective of its diagnostic role. (B)
- HRCT scanning should be performed on appropriate equipment. At least once a week checks should be made with a phantom to ensure the equipment gives high quality images. (C)
- Wherever possible an extended interscan interval (20 mm) and a low dose technique should be used. (C)
- The radiologist performing the HRCT scans should have expertise in the technique and recognise the strengths and limitations of the procedure. At least one radiologist in any department should have a declared interest and be trained in chest radiology and HRCT scanning. (C)
- Consideration should be given to establishing a reference panel of radiologists with particular expertise in HRCT scanning. (C)
- DTPA scanning is being evaluated in the diagnosis and assessment of DPLD but is not currently recommended as a routine test. (C)
- Gallium scanning is not recommended in DPLD but is of occasional value in extrapulmonary sarcoidosis. (C)

Lung function

- While most patients will have restrictive lung function, some DPLDs are associated with airflow obstruction or occur in patients with pre-existing airflow obstruction. A finding of airflow obstruction should not by itself lead to exclusion of a diagnosis of DPLD. (B)
- The minimum lung function assessment should be spirometric values and gas transfer factor, which together give a reasonable measure of the extent of the disease. Vital capacity and gas transfer factor are the most appropriate lung function tools for disease monitoring. (B)
- Respiratory exercise testing should be considered in patients in whom DPLD is still suspected after a normal HRCT scan and static lung function. It may also help to suggest or exclude the possibility of DPLD in breathless patients in whom there are no clear pointers to a diagnosis of DPLD. Facilities for exercise testing should therefore be within easy access of all respiratory physicians. (C)
- When a diagnosis of DPLD has already been made from other assessments, there is inadequate evidence as to whether exercise testing is of further value in management. For the present, exercise testing is not recommended routinely. (C)
- The BTS should establish the most appropriate methodology for exercise testing and the most clinically important parameters derived from such testing. (C)

Bronchoalveolar lavage (BAL)

- BAL should be performed routinely in patients in whom malignancy or opportunist infection is being considered. BAL should be considered in other conditions such as suspected occupational lung disease or alveolar proteinosis. (B)
- BAL should be readily available to all respiratory physicians assessing a patient with suspected DPLD. (B)
- BAL should be performed according to published guidelines. (C)
- The added value of differential cell counts in BAL fluid is uncertain. A network of centres with expertise in the perfomance and analysis of BAL fluid samples should be established to answer important questions about the clinical value of this technique. (C)

Biopsy techniques and pathology

- Pathologists and respiratory physicians should meet regularly to review biopsy samples from patients with DPLD. (C)
- It should be standard practice to take lung biopsy samples in DPLD when the diagnosis remains uncertain after clinical and radiological assessment, unless there are patient contraindications or when the samples are very unlikely to contribute to management. (B)
- When small tissue samples are likely to provide a diagnosis (as in sarcoidosis and malignancy), transbronchial lung biopsy (TBLB) samples should be taken. (B)
- In patients with suspected sarcoidosis endobronchial biopsy samples should also be taken, particularly if difficulty is found in obtaining adequate TBLB samples. (C)
- TBLB samples should only be taken by a bronchoscopist experienced in the technique, or by a trainee under the direct supervision of such a bronchoscopist. (C)
- TBLB samples must be taken in line with previous BTS recommendations on bronchoscopy. (C)
- TBLB samples must be taken only with a normal coagulation screen and platelet count. It is a day case procedure. Fluoroscopy is not required. Four to six adequate biopsy samples should be taken from one lung. (B)
- The pathological report must be considered in relation to the clinical setting. A normal TBLB sample, or one showing non-specific inflammation or fibrosis, should be considered non-diagnostic. (B)
- In the diagnosis of conditions such as CFA, vasculitis, lymphoma, lymphangioleiomyomatosis (LAM), or Langerhans' cell histiocytosis (LCH) open lung biopsy (OLB) samples or video-assisted thoracoscopic (VATS) biopsy samples should be taken if a histological diagnosis is required. (B)
- As with TBLB samples, open lung or VATS biopsy samples showing non-specific inflammation or fibrosis with no characteristic features of CFA should be reported as non-diagnostic. (B)
- OLB and VATS biopsy samples are equally effective in providing tissue for histological examination. VATS is preferred in stable patients. OLB is the procedure of choice in ventilated patients. (B)
- HRCT scanning should be used to guide the site of OLB or VATS biopsies. (B)
- Percutaneous biopsies are not recommended for DPLD in general, but may be appropriate when there are focal peripheral infiltrates. (B)
- Wherever possible, biopsy samples from patients with DPLD should be examined by a pathologist experienced in respiratory pathology. (C)
- A reference panel of pathologists with experience in the diagnosis of DPLD should be established. (C)

Training/education

- Where two or more respiratory physicians work in a team, one physician should have a declared interest in DPLD and take the lead in developing services for such patients. (C)
- Training in the management of DPLDs should be a required part of specialist registrar training. (C)
- Consideration should be given to establishing a national network of centres with an interest and expertise in DPLD to promote best practices and research in the field. (C)
- TBLB and BAL are specialised procedures. The BTS should give consideration to the minimum number of procedures to be performed by trainees before they are considered accredited in such techniques. (C)
- Laboratory pulmonary function testing should be performed by trained lung function technicians. The BTS should establish minimum standards for the training of such technicians. (C)
- The BTS and ARTP have developed standards for the performance of lung function tests, and are currently working on standards in exercise testing. All lung function laboratories should adhere to such standards and be subject to national quality control. (C)
- Ideally respiratory physicians, radiologists, pathologists, and thoracic surgeons should meet to review the clinical course, imaging, and biopsies of patients with DPLD. As a minimum there should be meetings between respiratory physicians and radiologists, and between respiratory physicians and pathologists, as indicated above. (C)
- VATS and OLB are procedures with considerable potential for morbidity and mortality and should be performed only by thoracic surgeons with expertise in the field. (C)

Background literature review

Clinical evaluation

CLASSIFICATION

The DPLDs comprise over 200 entities[4] and include a wide spectrum of diseases, many uncommon and many of unknown aetiology. There is no universally agreed classification of DPLDs. Clinically, however, the diseases have similar presentations with increasing shortness of breath and widespread shadowing on the chest radiograph. While the focus of this review is on DPLDs that present with a subacute or chronic onset, there is overlap with those presenting acutely. As clinical assessment is the starting point for the management of these disorders, the whole spectrum of DPLDs is presented here.

They can be classified into:

1. Acute DPLD (table 1).
2. Episodic DPLD, all of which may present acutely (table 2).
3. Chronic DPLD due to occupational or environmental agents (table 3) or drugs (table 4).
4. Chronic DPLD with evidence of systemic disease (table 5).
5. Chronic DPLD with no evidence of systemic disease (table 6).

Epidemiology

Epidemiological data on DPLD are sparse. The annual incidence of chronic DPLD in New Mexico was found to be 31.5 per 100 000 in men and 26.1 per 100 000 in women.[5] The prevalence of cryptogenic fibrosing alveolitis (CFA) has been reported to range from 6 per 100 000 to 14.6 per 100 000.[5 6] The incidence of CFA increases markedly with age, being 160 per 100 000 in those of 75 years of age and older.[5] Deaths in England and Wales attributed to CFA rose from 336 in 1979 to 1035 in 1996,[7] with mortality rates increasing sharply with age.[8] CFA and sarcoidosis are probably the most common chronic DPLDs.[5]

Table 1 Acute DPLD

Cause	*Example*
Infection	Bacterial (including tuberculosis) Viral (e.g. chicken pox, measles) Fungal (e.g. invasive aspergillosis, histoplasmosis. associated with immunodeficiency, e.g. *Pneumocystis* and cytomegalovirus)
Allergy	Drugs* (e.g. penicillin) Fungi (e.g. aspergillosis) Helminths (e.g. *Toxocara*)
Toxins	Drugs* (e.g. cytotoxics, amiodarone) Toxic gases, fumes (e.g. chlorine)
Haemodynamic	Left venticular failure*, fluid overload, renal failure
Vasculitis/haemorrhage*	Goodpasture's syndrome, idiopathic haemosiderosis, Behcet's syndrome, systemic lupus erythematosus, Wegener's granulomatosis, Churg-Strauss syndrome
ARDS	Trauma, septicaemia
Unknown	Cryptogenic organising pneumonia*, cryptogenic pulmonary eosinophilia*

After reference 39.
*May also present with chronic disease.

Table 2 Episodic DLPD

Eosinophilic pneumonia
Vasculitides/pulmonary haemorrhage
Churg-Strauss syndrome
Extrinsic allergic alveolitis
Cryptogenic organising pneumonia

Clinical assessment

This involves a combination of history and examination, laboratory investigations, pulmonary physiology, imaging, bronchoalveolar lavage, and histological examination. A recommended algorithm for the diagnosis of DPLD is shown in fig 1.

History and examination

LENGTH OF HISTORY

It is first necessary to establish whether the disease is acute (table 1), episodic (table 2), or chronic (tables 3–6). The acute diseases generally have a history of less than three weeks. The length of time symptoms have been present is therefore very important. Every effort must be made to review all previous chest radiographs or, failing this, reports. Radiographic abnormalities may have been present for much longer than the symptoms, thereby identifying the condition as chronic. Episodic shadowing on the chest radiograph narrows the diagnostic field (table 2). However, there is considerable variation in the time course of presentation of many DPLDs. For example, eosinophilic pneumonia,[9] cryptogenic organising pneumonia (COP),[10] and Wegener's granulomatosis[11] may present acutely, episodically or chronically. Others such as drug-induced DPLDs may be acute or chronic.[12]

OCCUPATIONAL, ENVIRONMENTAL AND TRAVEL HISTORY

The range of occupational exposures associated with the development of DPLD is very broad and includes avian, animal and fish proteins, fungal spores, asbestos, silica, cobalt, beryllium, aluminium, isocyanates, copper sulphate, and sodium diazobenzene sulphate. Most agents relate to specific occupations but some, such as asbestos and silica, may be encountered in different occupational settings. It is not sufficient to record an occupational history as a job title. A detailed history of the occupational process, the exposure levels that are likely to have been experienced, and the provision and type of respiratory protection provided should be taken in both working and retired patients. Actual exposure measurements may be available from the industry concerned. Similarly, attempts should be made to obtain previous measurements of lung function and chest radiographs from occupational settings or previous hospital investigations. In cases in which it is uncertain whether occupa-

Table 3 Chronic DPLD secondary to occupational or environmental agents

Agent inhaled	*Example*
Inorganic dusts	
Fibrogenic	Asbestosis
	Silicosis
	Coal workers' pneumoconiosis
	Hard metal (cobalt)
	Aluminium lung
Non-fibrogenic	Siderosis (iron)
	Stannosis (tin)
	Baritosis (barium)
	Antimony
Granulomatous/fibrogenic	Berylliosis
Organic dusts (extrinsic allergic alveolitis)	
Bacteria	Farmers' lung (Thermoactinomycetes in mouldy hay)
	Bagassosis (Thermoactinomycetes in mouldy sugar cane)
Fungi	Suberosis (in cork workers)
	Cheese workers' lung (mouldy cheese)
Animal protein	Bird fanciers' lung (avian protein on feathers)
Chemicals	Pyrethrum extrinsic allergic alveolitis
	Isocyanates

Table 4 Drug and toxin induced DPLD: classification with examples

Antibiotics	Nitrofurantoin, sulphasalazine
Anti-inflammatory agents	Gold, penicillamine, aspirin
Cardiovascular agents	Amiodarone
Chemotherapeutic agents	Bleomycin, methotrexate
Drug induced SLE	Hydrallazine
Illicit drugs	Heroin, methadone, talc
Miscellaneous	Oxygen, radiation, lipoid pneumonia

After reference 40.

Table 5 Examples of chronic DPLD with evidence of systemic disease

(A)	Connective tissue disorders	
	Systemic sclerosis	Rheumatoid arthritis
	Systemic lupus erythematosus	Polymyositis
	Sjogren's syndrome	Mixed connective tissue disorders
	Ankylosing spondylitis	Behcet's disease
(B)	Neoplastic	
	*Lymphoma	*Lymphangitic carcinoma
	Micrometastates	
(C)	*Vasculitis	
	Wegener's granulomatosis	Microscopic polyangiitis
	Goodpasture's syndrome	
(D)	*Sarcoidosis	
(E)	Inherited disorders	
	Tuberose sclerosis	Neurofibromatosis
	Lipid storage disease	Hermansky-Pudlak syndrome
(F)	Other miscellaneous	
	Inflammatory bowel disease	HIV associated
	Post bone marrow transplantation	*Amyloidosis
	*Cryptogenic organising pneumonia	Miliary tuberculosis
	*Langerhans' cell histiocytosis	*Pulmonary eosinophilia

*May be confined to the lung.

Table 6 Examples of chronic DPLD with no evidence of systemic disease or external agent exposure

Cryptogenic fibrosing alveolitis	*Sarcoidosis
*Cryptogenic organising pneumonia	*Langerhans' cell histiocytosis
*Alveolar proteinosis	Bronchocentric granulomatosis
Chronic aspiration	Pulmonary veno-occlusive disease
Alveolar microlithiasis	Idiopathic pulmonary haemosiderosis
Lymphangioleiomyomatosis	Bronchoalveolar carcinoma
*Pulmonary eosinophilia	

*May be associated with systemic disease or external agents.

tional exposures are relevant, advice from a respiratory physician with expertise in occupational disease should be considered. Hobbies and pastimes should be reviewed, with specific enquiry as to exposure to birds. Keeping budgerigars or pigeons is the commonest form of exposure. Parasites may cause pulmonary eosinophilia and therefore a travel history should also be taken.

OTHER IMPORTANT PAST HISTORY

A past history of cancer and radiotherapy should be sought. Patients with basal crackles due to chronic DPLD will frequently have been prescribed diuretics for an erroneous diagnosis of heart failure. A lack of response to diuretics is usual in chronic DPLD but does not exclude cardiac failure. A cardiac history and evaluation is therefore crucial. A past and current history of asthma and rhinitis is invariable in Churg-Strauss syndome.

Individuals with opportunist infections, neoplasms, or other conditions relating to immunodeficiency (HIV positive or otherwise) can present subacutely with diffuse lung shadowing on the chest radiograph. Risk factors for HIV should be sought (homo/bisexual, intravenous drug administration, blood transfusion, blood products, HIV positive mother, unprotected sex). Patients with other forms of immunodeficiency (non-HIV) may have obvious predisposing features such as cytotoxic or immunosuppressant therapy for transplantation, neoplasm, or collagen vascular disease. However, there may be no obvious risk factors for HIV infection and the less common immunodeficiency syndromes may not have clear clinical pointers. A high index of clinical suspicion is therefore necessary.

FAMILY, SMOKING AND DRUG HISTORY

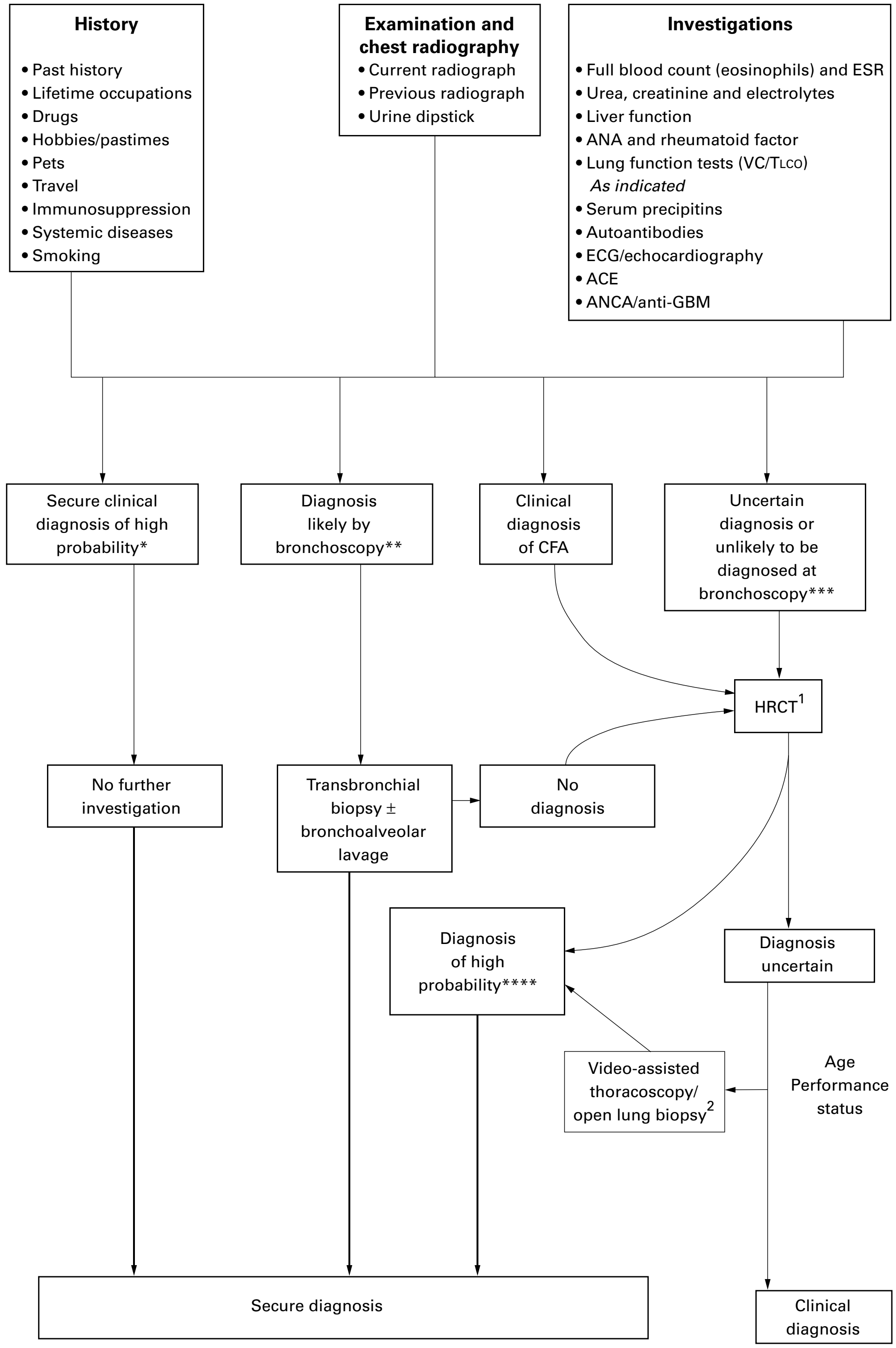
CFA and sarcoidosis may rarely be familial.[13 14] Patients with Langerhans' cell histiocytosis (LCH) and Goodpasture's syndrome are almost always smokers.[15 16] By contrast, patients with extrinsic allergic alveolitis and sarcoidosis are less likely to be smokers than the general population,[17 18] but the differences are not large enough to be helpful diagnostically.

A careful drug history is vital as many classes of drugs cause DPLD (table 4).[19 20] The variable timing of onset of symptoms from drug related DPLD has already been noted. Some drugs such as cyclophosphamide and amiodarone may have been taken for up to several years before such reactions develop.[19 20]

RESPIRATORY SYMPTOMS AND SIGNS

Most DPLDs present with shortness of breath but cough may be prominent, particularly in lymphangitic carcinoma, sarcoidosis, COP, CFA, extrinsic allergic alveolitis, and eosinophilic pneumonia. Other chest symptoms are uncommon but, if present, are important and may strongly suggest various diagnoses. Pleurisy may occur in the course of systemic lupus erythematosus (SLE) in up to 50% of cases and in 25% of cases with rheumatoid arthritis, but it is rare in CFA. Acute chest pain secondary to a pneumothorax occurs at some point in up to 40% patients with LCH, tuberose sclerosis, neurofibromatosis, or lymphangioleiomyomatosis (LAM). Haemoptysis is often, but not always, present in patients with pulmonary haemorrhage and vasculitis. It is unusual in cases of lymphangitic carcinoma unless there is primary lung cancer. Wheezing may occur in eosinophilic pneumonia because many patients also have asthma.

Bilateral fine end inspiratory crackles are common in CFA, fibrosing alveolitis associated with connective tissue disease, and asbestosis, occurring in 60% in two series[21 22] but generally reported in at least 90% of patients with



* Bilateral hilar lymphadenopathy ± erythema nodosum
Relevant occupational exposure and chest radiography
Pulmonary eosinophilia
Some drugs
Secondary cancer

** Sarcoidosis
Infection
Malignancy
Organising pneumonia

*** Fibrosing alveolitis
Langerhans' cell histiocytosis
Lymphangioleiomyomatosis

**** HRCT scanning is likely to yield a diagnosis of high probability for:
- Fibrosing alveolitis/asbestosis
- Lymphangitic carcinoma
- Sarcoidosis
- Subacute extrinsic allergic alveolitis
- Silicosis
- Lymphangioleiomyomatosis
- Alveolar proteinosis
- Langerhan's cell histiocytosis

[1] Some specialist centres also use bronchoalveolar lavage at this point as an adjunct to diagnosis and assessment of DPLD.

[2] Transbronchial lung biopsy may still be appropriate if HRCT scan suggests diagnosis likely to be made by bronchoscopy (see text).

Figure 1 Recommended algorithm for the diagnosis of DPLD.

CFA.[23 24] Crackles are much less common in sarcoidosis and extrinsic allergic alveolitis (25% or less)[22 25] and LCH (10%).[22] Wheezes or squeaks may be heard if bronchiolitis is present. Finger clubbing is seen in 49–66% of patients with CFA,[2 23] in up to 75% of patients with DPLD due to rheumatoid arthritis,[26] but less often in asbestosis (43% of cases in one series[27]) and in other DPLDs. Signs of pulmonary hypertension should be sought, particularly in systemic sclerosis. In patients with severe disease tachypnoea at rest, cyanosis, and signs of cor pulmonale may be present.

SYSTEMIC SYMPTOMS AND SIGNS

Systemic symptoms and signs should be sought (table 7). Fatigue and some weight loss are common but non-specific. Significant weight loss suggests malignancy but may occur with any severe DPLD. Systemic features that suggest the possibility of HIV disease include dramatic weight loss, a background of generalised ill health, unexplained diarrhoea, generalised lymphadenopathy, oral candidiasis, and cutaneous Kaposi's sarcoma.[28 29]

Initial blood and other tests

The minimum initial investigations are urine dipstick, full blood count and eosinophil count, urea, electrolytes and creatinine, liver function tests, and auto-antibodies (ANF and RF). If vasculitis is suspected, the titres of anti-neutrophil cytoplasmic and anti-basement membane antibodies should also be measured. If the differential diagnosis includes sarcoidosis, serum calcium levels should be measured as they were found to be raised in 11–18% of patients in large European studies.[30]

Serum angiotensin converting enzyme (ACE) has a diagnostic sensitivity of only 60% and poor specificity.[30 31] While it has been considered useful in long term management,[30] it does not correlate with radiographic stage and hence prognosis,[32] and does not add to the predictive value of serial pulmonary function testing and chest radiography in the management of the disease.[33] The routine measurement of serum ACE levels is not recommended.

If extrinsic allergic alveolitis (EAA) is suspected, serum should be tested for precipitins to environmental allergens—for example, avian proteins, *Micropolyspora faeni*, and *Thermoactinomyces vulgaris*. Precipitins are markers of antigen exposure and do not seem to be involved in the pathogenesis of the disease. While most pigeon breeders and farmers with EAA have serum precipitins,[34] the selectivity is very poor with precipitins being found in up to 50% of asymptomatic pigeon breeders[35 36] and 8–10% of asymptomatic farmers.[35] The available evidence does not support routine testing for precipitins in patients with DPLD.

In the United Kingdom there is a national quality control system for all these investigations except anti-basement membrane antibody.

Echocardiography should be performed in patients with systemic sclerosis to assess pulmonary hypertension and in cases where there is doubt as to whether heart failure may be the cause of diffuse shadowing on the chest radiograph. Electrocardiography should be performed in patients with sarcoidosis.

The technique of induced sputum can diagnose *Pneumocystis carinii* pneumonia (PCP) in up to 50% of HIV positive patients.[37 38] This approach requires meticulous technique, is time consuming, and requires special laboratory skills. It is therefore suitable only for centres handling large numbers of such patients.

Table 7 Systemic signs and DPLD

Fever	Infections (including immunodeficiency), eosinophilic pneumonia, drug reactions, vasculitis, connective tissue disorders, cryptogenic organising pneumonia, extrinsic alveolitis, sarcoidosis, AIDS, lymphoma and lymphangitic carcinoma
Rash	Sarcoidosis, connective tissue disorders, vasculitis
Scleritis	Sarcoidosis, connective tissue disorders, vasculitis
Keratoconjunctivitis sicca	Sjogren's syndrome
Uveitis	Sarcoidosis, Behcet's syndrome, ankylosing spondylitis
Raynaud's phenomenon	Systemic sclerosis, CFA
Systemic hypertension	Connective tissue disorders, Goodpasture's syndrome, vasculitis
Lachrymal and salivary gland enlargement	Sarcoidosis, Sjogren's syndrome
Lymphadenopathy	Sarcoidosis, lymphoma, lymphangitic carcinoma, HIV
Pericarditis	Connective tissue disorders, lymphangitis, lymphoma, vasculitis
Hepatosplenomegaly	Sarcoidosis, LCH, connective tissue disorders, amyloidosis
Arthritis	Connective tissue disorders, vasculitis, sarcoidosis, Goodpasture's syndrome
Haematuria	Vasculitis
Oral candidiasis	Immunodeficiency (especially HIV)

CFA = cryptogenic fibrosing alveolitis; LCH = Langerhans' cell histiocytosis.

Imaging in DPLD

HOW USEFUL IS THE CHEST RADIOGRAPH?

Patients with suspected DPLD will have a chest radiograph as the initial imaging investigation. In most cases this is abnormal and occasionally the radiographic appearances are sufficiently characteristic to enable a specific diagnosis to be made when taken in conjunction with the clinical and laboratory findings—for example, sarcoidosis, pulmonary eosinophilia, and some occupational lung diseases. In most patients, however, the chest radiographic pattern is not specific and the correct diagnosis will be made from the first two choices in only 50% of cases.[41]

In a small proportion of patients with open lung biopsy confirmation of DPLD the chest radiograph may be normal.[42] Conversely, the chest radiograph may be over read as abnormal when there is no histological evidence of DPLD.[43] The best kilovoltage peak (kVp) for the assessment of DPLD on the chest radiograph is 125.

WHAT IS THE ADDED VALUE OF HIGH RESOLUTION COMPUTED TOMOGRAPHIC (HRCT) SCANNING?

HRCT scanning is capable of imaging the lung with excellent spatial resolution and providing anatomical detail similar to that seen by gross pathological examination. The modifications of the CT technique which make it one of "high resolution" are the use of thin sections (collimation) and image reconstruction with a high spatial frequency algorithm. In addition, both kilovoltage peak and milliamperes are normally increased.

The added value of HRCT scanning in DPLD depends upon its ability to increase confidence of a specific diagnosis, to alter

Table 8 Typical HRCT appearances of some DPLDs

- Cryptogenic fibrosing alveolitis (CFA)
  Patchy abnormalities which predominate in the periphery of the lung and in the lower lobes
  Reticular and honeycomb changes often associated with ground glass opacification and traction bronchiectasis
- Asbestosis
  Very similar to CFA with abnormalities mainly in the subpleural region
  Reticulonodular opacities, thickened interlobular septa and honeycomb changes. Often associated pleural plaques
- Sarcoidosis
  Abnormalities tend to predominate in the mid/upper zones
  Micronodules with a bronchovascular and subpleural distribution
  Later there are conglomerate masses with lung distortion
  Commonly lymph node enlargement
- Lymphangitic carcinoma
  Irregular thickening of the interlobular septa. Peribronchial cuffing. Thickening of fissures. No architectural distortion
- Extrinsic allergic alveolitis
  Ground glass opacification and poorly defined centrilobular micronodules. Air trapping on expiratory scans. In late stage disease there are irregular linear and reticular opacities due to fibrosis
- Langerhans' cell histiocytosis (LCH)
  Cysts often of bizarre shape, associated with nodules. The lung bases are usually spared
- Lymphangioleiomyomatosis
  Thin walled cysts surrounded by normal lung. No zonal predominance.

patient management and, if possible, to influence outcome.

Detection of DPLD

HRCT scanning is able to detect DPLD not visible on the chest radiograph. The relative sensitivities of the two techniques for the detection of DPLD are 94% and 80%, respectively.[44] HRCT scanning is also better able than chest radiography to determine whether the lungs are normal.[45] Thus, increased sensitivity is matched by increased specificity.

Examples of the clinical usefulness of HRCT scanning in patients with symptoms of DPLD and a normal chest radiograph include the detection of occupational lung disease (such as asbestosis and EAA), early fibrosing alveolitis, and early lymphangitic carcinoma.[46 47]

Characterisation of disease and extent of disease

Several studies have compared the diagnostic value of chest radiography and HRCT scanning. They indicate that observer variability is lower with HRCT scanning than with chest radiography and that a confident diagnosis is more likely to be made and more likely to be correct with HRCT scanning.[45 48–51] CT interpretation is particularly accurate in fibrosing alveolitis, lymphangitic carcinoma, sarcoidosis, silicosis, subacute EAA, and alveolar proteinosis.[45 48 50] The diagnostic accuracy of HRCT scanning is further increased by concurrent clinical evaluation.[52]

Unlike chest radiography, HRCT scans provide cross sectional images and the extent of disease is therefore much more readily appreciated than on the chest radiograph. HRCT scanning may also elucidate patients with inexplicable or complex lung function abnormalities—for example, co-existing fibrosing alveolitis and emphysema.[53]

Impact on lung biopsy samples

HRCT scanning has a high degree of accuracy in many forms of DPLD. The percentage of first choice diagnoses made with a high level of confidence in two studies was 82% and 93%.[46 48] Fibrosing alveolitis may be confidently distinguished from other forms of DPLD with an accuracy of 88%.[54] Using Bayesian analysis, Grenier *et al* concluded that the combination of clinical, radiographic, and HRCT findings enabled a correct diagnosis with a high level of confidence in 61–80% of patients with DPLD.[52] On the basis of these findings it is evident that HRCT scanning can prevent the need for a histological diagnosis, particularly when the HRCT appearances are characteristic and taken in conjunction with the clinical findings—for example, fibrosing alveolitis, sarcoidosis, EAA, asbestosis, lymphangitic carcinoma, LAM, LCH (table 8).[55] Some caution is required, however, as prospective data on the diagnostic accuracy of HRCT scans in unselected populations are still lacking.

In considering the need for histological confirmation of DPLD, it is evident that the accuracy of the CT diagnosis is highly dependent on the experience and interest of the reporting radiologist. The extent to which HRCT scanning precludes the need for biopsy samples to be taken in routine clinical practice is not known.

For patients in whom lung biopsy samples are required, HRCT scanning is better able to differentiate between the need for transbronchial biopsy or open lung biopsy samples,[48] and is also able to determine the most appropriate areas from which the biopsy samples should be taken.[56]

Assessment of disease activity

Research on the ability of HRCT scans to differentiate between active and inactive disease has been mainly confined to CFA and fibrosing alveolitis associated with systemic sclerosis. There is evidence that a predominant ground glass pattern is more likely to represent active inflammatory disease and to respond to appropriate therapy, particularly in fibrosing alveolitis, EAA, and desquamative interstitial pneumonia.[57–61] It is still unproven that a ground glass pattern precedes a reticular or honeycomb pattern, although this seems likely. Not all ground glass change indicates cellular inflammation, however, as fine intralobular fibrosis may be indistinguishable from a cellular infiltrate on HRCT scans.[60 62] The association of a ground glass pattern with traction bronchiectasis or bronchiolectasis is likely to indicate some associated fibrosis, whereas ground glass change without traction bronchiectasis usually indicates active inflammation.[62] Reticular and honeycomb patterns on HRCT scans correlate well with histological evidence of fibrosis.[58 63]

Prediction of response to treatment

Because of its ability to differentiate between cellular and fibrotic disease with reasonable accuracy, HRCT scanning can be used to predict response to treatment and is significantly more accurate than chest radiography in this respect.[57 61] In treated patients with CFA improvement in lung function in those with a predominantly ground glass pattern is significantly better than in those with a reticular pattern or a mixture of ground glass and reticular patterns. This improved response rate is matched by improved survival, the predictive value of the HRCT scan being independent of lung function or duration of breathlessness.[57] The extent of fibrosis on HRCT scanning showed 80% sensitivity and 85% selectivity in predicting survival.[64] In patients with rapidly deteriorating CFA early evidence suggests that the appearance of peripheral as opposed to multifocal or diffuse parenchymal opacification on the HRCT scan predicts a better response to steroid treatment and survival.[65]

Radiation dose

The skin radiation dose from HRCT scanning using thin sections (1–2 mm) at 10 mm intervals is approximately 0.7 mSv. This is approximately 10% of the dose of conventional CT scanning using 10 mm slices at 10 mm intervals.[66] If HRCT scanning is performed at 20 mm intervals the effective dose is 0.35 mSv. In radiation terms this is the equivalent of approximately seven postero-anterior chest radiographs (for which the effective dose is 0.05 mSv). A significant reduction in radiation dose is also possible without substantial impact on image resolution by the use of lower milliamperes.[67] Combining a low dose technique with a limited number of slices provides greater accuracy than chest radiography with no significant increase in effective radiation dose.[68] As there is the potential for a high dose of irradiation from CT scanning, all units should have regular quality assurance checks and doses should be monitored periodically and compared with national standards.

Imaging: conclusions

- Using HRCT scanning rather than radiography, clinicians are significantly more likely to determine the correct diagnosis for DPLD, the extent of the disease, and the optimal site from which biopsy samples should be taken.
- A combination of clinical and HRCT information enables a correct diagnosis to be made in up to 80% of patients with DPLD.
- In the appropriate clinical setting, lung biopsy samples may not be required when the appearance of the HRCT scan is characteristic.
- HRCT appearances are also of value in determining disease activity and, in CFA, patients' prognosis.
- HRCT is a specialised technique. Interpretation of HRCT images requires particular skills on the part of the radiologist together with a proper understanding of DPLD.
- Radiologists who perform and report HRCT examinations should ensure that they have the necessary expertise and meet regularly with respiratory physician colleagues to review imaging from patients with DPLD.

GALLIUM SCANNING AND OTHER IMAGING TECHNIQUES

Gallium scanning was used in the 1980s as an investigation that was thought to be sensitive for the identification of DPLDs such as sarcoidosis, and was believed to be of prognostic value.[69–71] Gallium scans can be diagnostically helpful where other investigations are not diagnostic in sarcoidosis, but its value in CFA has never been proved. Furthermore, the pulmonary parenchyma may be positive in a wide range of DPLDs and, in this context, gallium scanning is not helpful. Gallium scans have also been evaluated in pulmonary HIV disease and add nothing to other diagnostic techniques.[72] Serial gallium scans are not useful as monitors of disease in CFA.

Gallium scanning is expensive and involves the patient making two hospital visits (one for injection and one for scanning). Quantification is often imprecise and the technique is associated with radiation exposure. The procedure should be restricted to situations in which the diagnosis of DPLD (unspecified) is suspected and for which further evidence is required.

Imaging with radiolabelled indium-111 neutrophils is being used in research studies to demonstrate neutrophil traffic to the lungs. Radiolabelled indium-111 transferrin is also being explored as a measure of pulmonary vascular leak. Positron emission tomography (PET) has been used to identify increased metabolic activity within the lung in fibrosing alveolitis. The role of magnetic resonance imaging (MRI) in identifying early inflammation in the lung is also being investigated. All of these techniques may establish themselves in the future as investigations in DPLD. At present, however, they should be reserved for research studies.

Gallium scanning: conclusions

- Gallium scanning and other imaging modalities such as PET and MRI have little place in the diagnosis or management of DPLD.
- Gallium scanning may have a role in suspected extrathoracic sarcoidosis which is not accessible to biopsy sampling.

Lung function and exercise testing in DPLD

LUNG FUNCTION TESTING AND DIAGNOSIS OF DPLD

DPLDs are usually thought to be characterised by restrictive lung function, by which is meant a reduction in lung volumes with preserved ratio of forced expiratory volume in one second

(FEV_1) to forced vital capacity (FVC) together with a reduction in carbon monoxide transfer factor (TLCO). However, in early disease lung volumes and transfer factor may be within the normal range.[73] Furthermore, in sarcoidosis evidence of airflow obstruction has been found in more than half the patients in some studies,[74 75] the prevalence increasing with radiographic stage, but in only 11% of non-smokers at presentation in another study.[76] Airflow obstruction is found at presentation in 4–33% of patients with LCH[77 78] and in 65–78% of patients with LAM.[79 80] Lung volumes may be relatively preserved in smokers with CFA,[53 81 82] possibly due to coexisting emphysema,[53 81] although the FEV_1/FVC ratio remains normal.[53 81–83] These findings suggest that it is inappropriate to use restrictive lung function as an exclusive diagnostic criterion. The sensitivity and specificity of routine lung function tests in populations of patients with a diagnosis of DPLD established by other means are not known.

In systemic sclerosis an isolated reduction in TLCO may point to pulmonary vascular disease. In one study 19% of patients had such lung function, 11% of whom developed isolated pulmonary hypertension, the risk increasing markedly with lower TLCO.[84]

In DPLD in immunodeficiency, lung function tests do not generally have a diagnostic role.[85] Patients may often be too ill to perform the tests and the investigations lack the appropriate sensitivity and specificity to be of diagnostic value. However, the negative predictive value of a normal TLCO for the presence of PCP in HIV infection is extremely high—that is, if the TLCO is normal, the presence of PCP is virtually excluded.[86]

Of the various indices derived from exercise testing, an increased alveolar-arterial (A–a) oxygen gradient is a more sensitive indicator of the presence of various DPLDs[87] and sarcoidosis[88 89] than conventional lung function tests. Abnormalities of gas exchange during exercise may be found in subjects with DPLD and normal resting lung function, and such abnormalities are not predictable by measurements taken at rest.[87] In HIV positive patients with symptomatic DPLD but normal resting arterial oxygen saturation, desaturation on simple exercise testing has good specificity for PCP.[90 91] In general, however, the role of exercise testing in the diagnosis of DPLD is uncertain, but it has been useful in the detection or exclusion of DPLD in symptomatic patients with a normal chest radiograph and resting lung function.[92] However, the sensitivity and specificity of exercise testing for the diagnosis of DPLD in this respect are unknown, and if occult DPLD is suspected as the cause of breathlessness in such patients most will currently go on to HRCT scanning. No studies have assessed the diagnostic value of exercise testing in comparison with HRCT scanning.

Lung function testing and diagnosis: conclusions

- The usefulness of lung function testing in the diagnosis of DPLD is limited.
- A restrictive pattern of lung function is probably the commonest pattern, but a proportion of patients have preserved lung volumes or airflow obstruction. Such abnormalities should not lead to the exclusion of a diagnosis of DPLD.
- The literature suggests that the role of exercise testing in the diagnosis of DPLD is probably limited to the detection or exclusion of occult DPLD as the cause of breathlessness in some patients with a normal chest radiograph and lung function. There is no evidence as to the relative value of exercise testing and HRCT scanning in this situation.

SEVERITY AND PATTERN OF DISEASE

Lung function tests are conventionally used to give a global index of functional impairment. Vital capacity (VC), total lung capacity (TLC), and TLCO are most commonly used while, in the UK, exercise testing is used relatively little. Several studies have correlated lung function and exercise test parameters with the degree of pathological abnormality on lung biopsy samples using the latter as the gold standard.

Fulmer *et al*[93] found that TLC, TLCO, and oxygen tension (PaO_2) at rest did not correlate with either the degree of fibrosis or cellularity in patients with CFA, while both exercise induced changes in PaO_2 and the A–a oxygen gradient were highly correlated with fibrosis and reasonably so with cellularity. VC and pulmonary compliance correlated with fibrosis, though not with cellularity.[93] These and other data led to the view that gas exchange on exercise gave a better indication of overall disease extent than lung volumes or TLCO.[88] However, other studies have reported different findings. In untreated patients with CFA both gas transfer (TLCO, not KCO) and lung volumes strongly correlated with the extent of fibrosis and cellular infiltration, and more strongly so than gas exchange on exercise.[94] Other studies suggest that TLCO is a predictor of exercise test abnormalities.[95 96]

In sarcoidosis TLCO (particularly) and VC correlate with the overall severity of pathological change, but only TLCO and PaO_2 on exercise parallel both the degree of fibrosis and granulomatous involvement.[97]

Neither lung function nor exercise test parameters discriminate between fibrosis and inflammation in CFA.[88 93 94]

Watters *et al*[98] developed a composite clinical radiographic physiological (CRP) score using seven variables: dyspnoea, chest radiograph, FEV_1 and FVC, TLC, TLCO/VA, resting A–a gradient, and exercise oxygen saturation. The CRP score correlated well with an overall pathology score and better than any of its component parts. The CRP score is further discussed below.

Severity of disease: conclusions

- Simple lung function testing using lung volumes and gas transfer factor gives a reasonable measure of the extent of disease.

- The evidence that exercise testing provides additional useful information as to overall severity is conflicting.
- Lung volumes, gas transfer factor, and exercise parameters, considered either separately or together, do not discriminate between inflammation and fibrosis.

MONITORING THE COURSE OF DISEASE

There is little information on the use of serial lung function tests in managing disease or on the value of "one off" tests in predicting treatment response or prognosis.

In CFA Agusti *et al*[96] found that both the carbon monoxide transfer coefficient (KCO) and the increase in A–a gradient on exercise at initial assessment correlated reasonably with the increase over three years in A–a gradient at rest. However, this study had only one outcome measure—that is, the ability to be able to predict the change in A–a gradient at rest (not on exercise) over three years. All patients in the study had received steroid treatment, therefore allowing no analysis of treatment effects. Agusti *et al* suggested that exercise testing added further information but no convincing evidence is provided for this assertion.[96] Initial VC has been a predictor of survival in some studies[99–101] but not in others.[23 24 64 102] Likewise, TLCO has predicted survival in some studies[24 99 101] but not in the most recent study.[64] KCO or exercise testing do not predict survival.[102] In multivariate analysis an increased FEV_1/FVC ratio was the most important initial lung function predictor of survival.[99] Over one year of treatment, changes in FVC and TLCO are also strongly predictive of survival in CFA.[103]

In sarcoidosis changes in VC correlate better with radiographic improvement than TLCO[104] and the reverse is the case with radiographic worsening, with no additional information from exercise testing. Lawrence *et al*[105] studied 12 patients with sarcoidosis and found that the improvement in VC over six weeks paralleled clinical improvement better than TLC and TLCO, but this small study was mainly concerned with other markers of activity. VC is probably a more sensitive index of response to steroids overall, and there is no evidence that blood gas analysis/compliance testing adds useful information (see reference 104 for review). A small study suggested that monitoring VC over a three week trial of steroids is likely to show which patients are responsive.[106]

In the original evaluation of the CRP score, the correlation of a change in CRP score over six months of treatment with a pathological score at presentation reflecting cellularity was better (though not significantly so) than any of the component parts of the score including FVC and KCO.[98] Recently, the CRP score has been shown not to improve the ability of the HRCT appearances to predict mortality in CFA.[64] There has been relatively little published assessment of the value of the CRP score in monitoring disease in different populations and its place remains unclear.

Lung function in monitoring DPLD: conclusions

- VC and TLCO are the most appropriate and simplest indicators of change in DPLD.
- The evidence on whether these measurements can predict survival is contradictory.
- Inadequate data are available on the question of whether exercise testing offers additional information to VC and TLCO.
- Further prospective studies are urgently required as to the most appropriate measures for monitoring disease activity in DPLD.

Role of bronchoalveolar lavage

Bronchoalveolar lavage (BAL) to sample cells and non-cellular material from the lower respiratory tract has now been used for almost 20 years in the evaluation of DPLD.[107–109] Guidelines as to the performance of BAL are available.[110 111] The central current issues are whether BAL contributes to making a diagnosis in patients with DPLD and to the assessment of prognosis.

BAL AND DIAGNOSIS OF DPLD

In diseases such as those due to occupational exposures to inorganic dusts,[112–115] opportunist infection,[116 117] suspected malignancy, haematological disease and the sequelae of transplantation,[118–120] drug induced disease,[121–123] and some rare DPLDs such as alveolar proteinosis[124–127] and LCH[128–130] the BAL findings can be diagnostic.

In HIV disease BAL offers the most immediate way of establishing a diagnosis of DPLD and 70–90% diagnostic yields are reported, especially in PCP.[28 131] BAL in this situation is performed by wedging the bronchoscope in an appropriate segmental bronchus, usually the middle lobe, and instilling and aspirating between two and four 20–60 ml aliquots of warmed sterile normal saline.

In other DPLDs characterised by the accumulation of abnormal numbers of inflammatory cells in the lung the differential cell counts can detect subclinical disease, especially in the context of rheumatological disease.[132–137]

Diagnostically, the predominant inflammatory profile provides an indication of the nature of the underlying disease process. An increase in granulocytes, particularly neutrophils and eosinophils, in the BAL fluid is typical in cases of fibrosing alveolitis occurring alone or with rheumatological disease, asbestosis, and the adult respiratory distress syndrome.[107 108 111 133 138–141] Increased numbers of lymphocytes are associated with granulomatous and drug-induced DPLD.[111 119 142] In granulomatous disease diagnostic specificity increases with the use of CD4:CD8 lymphocyte ratios at the expense of sensitivity.[143 144] In a recent study a discriminant diagnostic model was generated from BAL cell counts in a population of patients with sarcoidosis, EAA, and CFA. The model was then tested on a second population and found to predict the correct diagnosis in 95% of cases.[145] However, no studies have been performed that assess whether BAL cell counts provide any useful information over and above that from HRCT scanning.

BAL AND PROGNOSIS OF DPLD

Patients with CFA with increased numbers of lymphocytes in the BAL fluid, with or without granulocytes, are more likely to respond to steroids.[107 146 147] In one study increased numbers of granulocytes without lymphocytes suggested a better responsiveness to cyclophosphamide than to prednisolone,[148] but serial BAL cell counts as a monitor of disease are clinically unhelpful.[148]

The predominant inflammatory cell is also an indicator of prognosis. More extensive disease in fibrosing alveolitis is associated with a poor prognosis[23 24] and BAL neutrophilia and/or eosinophilia is associated with more extensive disease and a poor prognosis.[107 139 146–153] However, in a multivariate analysis (which did not include HRCT information as a variable), BAL cell counts did not independently predict prognosis.[151 154]

BAL in diagnosis and prognosis: conclusions

- BAL is a useful diagnostic tool, particularly in suspected infection, malignancy, and some rare DPLDs.
- There are inadequate data as to the added value of BAL cell counts in diagnosis and prognosis in other DPLDs. Whether BAL cell counts should be performed routinely is therefore unclear. Further research on BAL counts should address this question.

^{99m}Tc-diethylenetriamine penta-acetate (DTPA) scanning

^{99m}Tc-DTPA aerosol clearance is an index of lung epithelial permeability. Increased permeability results from inflammation in the lung parenchyma in a variety of DPLDs such as fibrosing alveolitis, dermatomyositis, EAA, sarcoidosis, radiation pneumonitis, and pneumonconiosis,[155–170] often when there is little other evidence of DPLD. An increased DTPA clearance is a sensitive marker of inflammation and a normal clearance certifies absence of inflammation.[171]

In addition to its potential role in the detection of DPLD, DTPA scanning has been used as a measure of prognosis in sarcoidosis, fibrosing alveolitis, and asbestosis.[158 163 164] Persistently rapid clearance is associated with a higher risk of subsequent deterioration in lung function, but persistently normal clearance predicts disease stability. In HIV disease a biphasic pattern of clearance is seen in PCP with early rapid clearance of DTPA from the lung,[172] but the technique lacks specificity and adds little to other diagnostic techniques. A drawback of DTPA is that it cannot be employed in cigarette smokers as airway inflammation affects the clearance of the isotope.[173–176]

Serial studies of DTPA in fibrosing alveolitis and radiation induced fibrosis have concluded that DTPA measurements may predict trends that justify treatment of patients before symptoms develop.[164 177]

DTPA scanning: conclusions

- DTPA scanning may become important in the repertoire of investigations in certain DPLDs.
- Further studies are needed to establish its value in conjunction with other investigations such as HRCT scanning, particularly in rheumatological disease as an index of early lung involvement and in CFA as a measure of prognosis.
- Insufficient data are available to support the routine use of DTPA scanning in the assessment of DPLD.

Role of lung biopsy and pathology

Histological examination is usually performed in DPLD to assist diagnosis, although in CFA it has also been recommended by some authors to assess disease activity and the likelihood of treatment response.[21 178 179] Despite previous recommendations that histological examination should be routinely performed in DPLD,[179 180] transbronchial biopsy (TBLB) or open lung biopsy (OLB) samples were only obtained in 28–33% and 8–12% of patients, respectively, in two UK studies of CFA.[2 181] In the USA a questionnaire survey with a low response rate suggested that most physicians try to obtain a tissue diagnosis in DPLD,[3] but an epidemiological survey found that, as in the UK, in only a small proportion (11%) of patients with CFA had an OLB sample been taken.[5]

The usefulness of HRCT scanning in both diagnosis and assessment reduces the need for lung biopsy samples (see page S8) and influences the choice of biopsy technique. The advent of this technique in recent years now necessitates a reappraisal of the role of lung biopsy samples.

REVIEW OF BIOPSY PROCEDURES

The decision as to the type, size, and site of the biopsy sample is determined by the level of prebiopsy diagnostic certainty, the suspected nature, distribution and extent of the DPLD, and the patient's perfomance status. Some DPLDs show overlapping histological features and, for optimal diagnostic results, close liaison between the physician, thoracic surgeon, radiologist, and pathologist is important.

Transbronchial lung biopsy (TBLB)

Although TBLB samples were first obtained via a rigid bronchoscope,[197 198] they are now almost exclusively obtained via the fibreoptic bronchoscope. Sampling error is a problem and the specimens are often too small to enable a definitive diagnosis.[199 200] Crushing of the specimen and failure to penetrate beyond the peribronchial sheath may also preclude histological assessment. Alligator forceps produce bigger specimens than large and standard cup forceps but may be more likely to obtain bronchial wall samples and make no significant difference to the diagnostic yield.[201–203]

Despite these problems, TBLB achieves a high diagnostic yield in DPLDs with centrilobular accentuation such as granulomatous and metastatic diseases.[204–206] A high diagnostic yield can also be achieved in infection, alveolar proteinosis, and eosinophilic pneumonia. One report suggests that TBLB can also provide diagnostic material in 64% of patients with COP.[207]

In patients with sarcoidosis with diffuse infiltrates a diagnostic yield of 75–89% can be expected, and in carcinoma the yield is 64–68%.[204 206 208 209] A diagnosis is less likely in sarcoidosis (44–66%) when parenchymal disease is not visible on the chest radiograph.[206 208 210] Endobronchial biopsy samples in sarcoidosis are diagnostic in 45–77% of cases,[208 209 211] but whether such biopsy samples provide additional diagnostic information to that obtained from TBLB samples is not clear. The diagnostic rate is less good over the broad spectrum of DPLD with diagnostic information in 38–79% of cases[199 200 204 205 212 213] and, most recently, 50% in a large study.[206] In patients with CFA the TBLB specimens are too small and non-representative to allow either a reliable diagnosis or determination of the relative degree of cellularity and fibrosis.[199 200]

Multiple biopsy samples are required with the diagnostic yield rising from about 60% to 90% in radiological stage 2 sarcoidosis when the number of samples is increased from two to four.[214] In general, 4–6 biopsy samples achieve an overall good yield in DPLD.[206 215]

TBLB is a safe outpatient procedure.[216] Pneumothorax has been reported in up to 10% of cases but, more generally, the figure is 0.7–2% with about half requiring tube drainage.[198 204 206 217–219] The rate of pneumothorax was reduced by avoiding the right middle lobe and lingula and with the use of fluoroscopy.[198 219] However, other studies have shown that TBLB without fluoroscopy achieves similar results with regard to positive histological findings and the incidence of pneumothorax.[201 205] Bleeding occurs in 9% of cases[216] but this only exceeds 50 ml in about 1%.[198 204 218] Mortality is approximately 0.1% with haemorrhage the main cause.[219] Coagulation screening prior to TBLB is necessary practice.[217 220]

Open lung biopsy (OLB)

OLB by limited thoracotomy provides larger specimens than TBLB. In a large number of series the diagnostic yield was 94% compared with 72% with TBLB, 72% with drill, and 63% with needle biopsy.[200] OLB provided a diagnosis in up to 92% of patients who did not have a diagnosis achieved by other biopsy techniques.[200 221] In a prospective study of 20 consecutive patients with DPLD undiagnosed by non-invasive methods, all underwent aspiration and cutting needle biopsy, TBLB, and OLB. There was a 94% success rate with OLB compared with 59% with TBLB and 29–53% with needle biopsy.[222]

The complication rate is up to 7%, with a mortality due to the procedure of probably less than 1%.[221 223 224] The procedure takes about 30 minutes and the intercostal drain is in situ for approximately one day,[225] but with considerable individual variation. Conventionally, more than one specimen has been taken to include macroscopically normal lung adjacent to and remote from obviously abnormal sites, avoiding areas with the greatest involvement radiologically which more often show end stage fibrosis of no diagnostic value.[226] However, a recent study concluded that a single biopsy sample from an inflamed and least fibrotic area of the radiographically most involved lobe achieves the highest diagnostic yield.[227] HRCT scanning is useful to guide the selection of the biopsy site and is more accurate than chest radiography in predicting whether TBLB or OLB is the more appropriate procedure.[48 56]

Video assisted thoracoscopic (VATS) lung biopsy

VATS is carried out under general anaesthesia with the patient ventilated through a double lumen tube or with high frequency jet ventilation. A fibreoptic bronchoscope is passed through a 2 cm stab incision with two ancillary operating ports. Biopsy specimens are the same size as those from OLB. The diagnostic accuracy is comparable (86–95% with VATS compared with 93–100% with OLB).[228 229] The procedure takes about 40 minutes, similar to OLB,[228] and in uncomplicated patients perioperative morbidity, postoperative pleural drainage, and length of hospital stay appear to be less with VATS, though comparisons have not been randomised.[228–234] In ventilator-dependent patients, however, OLB is the appropriate procedure.[235]

There is controversy over whether the lingula or middle lobe (surgically easily accessible) are suitable sites for OLB or VATS biopsy procedures in patients with DPLD. It has been suggested that these sites should be avoided because biopsy samples often show non-specific fibrosis and vascular changes not seen elsewhere in the lungs.[226 236–239] However, in more recent studies of DPLD, both in immunocompromised and non-immunocompromised patients, the lingula and right middle lobe have given similar histological results to other sites.[227 240 241] Whichever site is selected, it is important to obtain an adequate size of specimen as the disease process may be focal and the diagnosis missed because of sampling limitation.[226 241] Biopsy samples showing end stage lung or minimal disease give no useful information as to the underlying diseae aetiology.

Percutaneous biopsy

A number of percutaneous techniques have been used to obtain lung biopsy samples. Initially these were for peripheral tumours[182 183] with subsequent modification for DPLD.[184] Diagnostic material in DPLD has been obtained in up to 78% of cases.[185] Morbidity was high with pneumothorax in up to 50%.[185–190] Air embolism and haemorrhage were less common sequelae but were more likely to be fatal with an overall mortality of 0.1–3.1%.[188 191–194] Small recent studies have given similar diagnostic rates but with lower morbidity and mortality.[195 196]

HANDLING OF LUNG BIOPSY SAMPLES

It is recommended that 4–6 transbronchial biopsy samples should be obtained and placed with minimal handling and without delay into buffered formalin.[206 242] Open biopsy samples and those obtained by VATS should be at least 4 cm in maximum diameter when inflated and include a depth of at least 1–1.5 cm. The biopsy sample should be handled with minimal trauma and sent fresh to the laboratory without delay so that it can be gently inflated with formalin using a syringe and a small gauge needle inserted through the pleura.[242] The technique of inflating open lung biopsy samples could also be carried out in theatre by trained personnel. In DPLD, frozen sections are only of value in suspected malignancy. It may be appropriate to freeze a small portion of the unfixed specimen for immunofluorescence techniques, but not at the expense of tissue needed for histological examination. Small pieces of fresh tissue can be taken for microbiology/virology as required. Immunohistochemical techniques, in situ hybridisation, and polymerase chain reaction (PCR) can all be applied to maximise the diagnostic yields.[243–245]

ASSESSMENT OF LUNG PATHOLOGY IN CFA

The diagnosis of CFA should be made only if characteristic histological features are present.[246] To overcome interobserver variation a panel of pathologists used a semiquantitative scoring system for assessment of inflammatory and exudative changes, fibrotic and reparative changes, and airway alteration in CFA.[247] There was agreement between pathologists in up to 64% of assessments and the results compared favourably with those obtained from a morphometric analysis of specific histological features.[247 248]

The value of such intensive analysis is not known. In CFA the added value of a biopsy sample as an independent predictor of prognosis has not been established. Single biopsy samples are unlikely to be representative of the disease process because of heterogeneity of the disease in different sites.[246] The relationship between biopsy results and prognosis was lost after controlling for age and sex in one study[23] and, although a pathological fibrosis score predicted mortality, an HRCT fibrosis score had greater sensitivity and selectivity in this respect.[64]

Lung biopsy and pathology in DPLD: conclusions

- Biopsy samples, when required, should be taken before the initiation of treatment.
- TBLB is the initial procedure of choice in those patients likely to have DPLDs in which small samples may be diagnostic—for example, conditions such as sarcoidosis and malignancy.
- Four to six TBLB specimens should be taken.
- Only specimens that contain abnormal alveolar tissue are likely to contribute to diagnosis, though such specimens may still be non-specific. TBLB specimens consisting of normal lung or bronchial tissue, or of fibrous tissue, should be regarded as diagnostically unhelpful.
- Endobronchial biopsy samples are frequently positive in suspected sarcoidosis, but it is not clear whether they add further information to TBLB. However, the morbidity of taking endobronchial biopsy samples is very low.
- TBLB showing non-specific pneumonitis, with or without fibrosis, may help in supporting a clinical impression of DPLD but should not be regarded as diagnostic.
- TBLB is not useful for the diagnosis or staging of CFA.
- Percutaneous needle biopsy samples should be reserved for focal lesions.
- Certain DPLDs such as CFA, LCH, LAM, vasculitis, and lymphoma cannot be reliably diagnosed with TBLB. OLB or VATS biopsy samples are necessary if histological examination is required.
- The diagnosis of CFA should be made only if characteristic histological features are present. In the absence of diagnostic features a biopsy sample should be reported as non-specific.
- In patients with suspected COP, TBLB samples should be taken initially and OLB/VATS biopsy samples considered if the TBLB sample is non-specific.
- OLB and VATS biopsy techniques are equally effective in providing tissue for histological diagnosis. VATS is preferred in stable patients. OLB is required if the patient is on a ventilator.
- Biopsy samples from the middle lobe or lingula may be taken provided they are of generous size, contain deep alveolar tissue, and are from a site involved by active disease as judged by HRCT scanning.

Part 2: Treatment of diffuse parenchymal lung disease

Part 2 reviews and provides recommendations on the treatment of two major DPLDs—CFA and sarcoidosis. A further section briefly reviews several other DPLDs, some rare, for which only anecdotal evidence is generally available on treatment. Finally, the indications for transplantation are presented.

Cryptogenic fibrosing alveolitis

There is a paucity of controlled trials of drug treatment in this disorder and none have been placebo controlled. Corticosteroids have been frequently tried and other immunosuppressants less so.

CORTICOSTEROIDS

Although corticosteroids have been used since the 1950s, there are no controlled trials comparing them with placebo, and no data as to whether survival or quality of life is improved.[249] Since 1970 there have been several retrospective reviews of treatment with steroids in which symptomatic improvement was reported in 41–57% of patients.[100 250] Objective improvement, defined as an increase in FVC of 10%[100 147 250] or 15%,[24] was reported in 16–37% of cases.[24 100 147 250] Two more recent studies compared prednisolone alone with prednisolone and either azathioprine or cyclophosphamide. In the prednisolone arm objective improvement in FVC or TLCO was found in 23–32% of patients.[251 252]

There is difficulty in interpreting such studies because (1) some studies included patients with connective tissue diseases, (2) the dose of prednisolone used varied even within the same study, (3) the proportion of patients followed up has been variable, and (4) there are differences as to how long the improvement has been maintained (some studies assessed initial improvement, others looked for improvement over one year).

Nevertheless, common features that such studies identified as being associated with a steroid response are female sex[100 147] and an increased cellularity of the biopsy sample.[21 24 100] A response to steroids has also been associated with improved survival.[24 100 147 250] However, it may be that such a response merely identifies a group with a better prognosis irrespective of steroids. Turner-Warwick *et al* also studied a substantial number of untreated patients and compared their survival with a treated group. The survival of the untreated group lay between that of a group of patients responding to steroids and a group not responding to steroids. Indeed, in their study there was no survival difference between the steroid treated group and the untreated group after controlling for age and sex.[250] Young age,[23 24] less advanced disease,[23 24 99 100 147] female sex[23 99] and a cellular biopsy sample[21 23] have also been associated with improved survival. However, in one study a cellular biopsy sample was no longer related to survival after controlling for age and sex.[23]

Two small randomised studies reported on the use of high dose methylprednisolone, neither finding clinical benefit at up to six months compared with conventional doses of oral prednisolone.[253 254] Methylprednisolone has recently been used in acute exacerbations of CFA with variable success according to the pattern of parenchymal opacification on the HRCT scan, but without comparison against oral prednisolone.[65]

Several further issues complicate the assessment of the place of steroids in the treatment of CFA.

(1) Does stability on treatment represent success? Few studies have addressed this issue, most defining steroid response as improvement in symptoms and lung function. In two studies the proportion of patients with stable FVC on prednisolone was 23%[251 252] and, in an earlier study, 12–19% were stable on treatment compared with 15% of an untreated group.[21]

(2) Does spontaneous improvement occur? Different histological subsets may have different prognoses.[255] Desquamative interstitial pneumonia (DIP) which is characterised by uniform appearances of macrophages in alveolar spaces and minimal inflammation with patchy ground glass shadowing on the HRCT scan may not be progressive,[256] and 22% were reported to improve without treatment.[21] By contrast, no reports indicate spontaneous improvement in the common type of CFA—namely, usual interstitial pneumonia (UIP)—which is characterised by patchy inflammation, fibrosis, and honeycombing.

(3) Side effects of steroids. In four studies serious side effects were reportedly due to steroids. The proportion of patients affected ranged from 19–26%[250 252] to two thirds[21] and a "large number".[251] Such differences may relate to the generally higher doses of steroids used in the USA[21 251] than in the UK (table 9).[250 252]

Table 9 Regimens of prednisolone used in CFA

Author	*Regimen used*
Stack[100]	20–40 mg/day for 2–8 weeks. Then stop or reduce to 5–10 mg
Carrington[21]	30–60 mg daily tapering to 20 mg maintained for 1 year
Turner-Warwick[250]	10–60 mg/day
Rudd[147]	40–60 mg for 4–6 weeks reducing to 15–30 mg on alternate days
Crystal[257]	1 mg/kg/day for 6 weeks tapering to 0.25 mg/kg/day
Tukiainen[24]	40 mg tapering to 10 mg/day over 3 months. At 6 months stop or continue 5–10 mg/day
Johnson[252]	>60 kg weight: 60 mg for 4 weeks reducing by 5 mg each week to 20 mg on alternate days. <60 kg: 1 mg/kg/d, and same schedule of reduction
Raghu[251]	1.5 mg/kg/day (max 100 mg) for 2 weeks, then reducing by 20 mg every 2 weeks to 40 mg, then reducing by 5–10 mg every 2 weeks to 20 mg or less

Corticosteroids and CFA: conclusions

- There has been no placebo controlled trial of steroids in CFA, so there is no direct evidence that steroids improve survival.
- A proportion of patients do respond in terms of symptoms (about 50%) and lung function (about 25%).
- Although a steroid response is associated with better survival, it is not clear if this is due to the treatment itself.
- There are no comparative data on dose regimens nor on the length of time for which steroids or other treatment should be used.

IMMUNOSUPPRESSANT THERAPY

Cyclophosphamide and azathioprine are the two most studied drugs. There have been no controlled trials of either drug against placebo. Furthermore, it is not always clear from studies that have used these drugs whether they have been used concurrently with prednisolone.

Cyclophosphamide

The only randomised controlled trial using cyclophosphamide compared low dose prednisolone (20 mg on alternate days) plus oral cyclophosphamide with high dose prednisolone.[252] The initial response rates were 24% and 32% in the two groups; after three years three of 21 patients in the group receiving cyclophosphamide/prednisolone had died compared with 10 of 22 receiving prednisolone alone. However, at 5–9 years there were 15 deaths in each group. The better survival at three years was largely attributed to higher lung volumes at the start of treatment.

In uncontrolled studies a response (>10% increase in VC over a defined period) has been reported in about half of patients (combining studies, 13 of 23),[147 258 259] although there was no response in any of seven patients in one study.[260] A probable cure with intravenous cyclophosphamide was reported in a case of fulminant CFA[261] and a further case report records DIP apparently responsive only to cyclophosphamide.[262] Pulse intravenous cyclophosphamide in 33 patients was reported to improve mean lung function in those surviving an initial six months.[263] Such data are difficult to interpret without controls. In a further study pulse cyclophosphamide was associated with stable lung function both in survivors and those who died, suggesting that lung function may be an unreliable predictor of mortality in end stage CFA.[264]

In another study responders to cyclophosphamide had previously responded to prednisolone[265] and, anecdotally, Lynch and McClune[266] reported that <15% of 80 patients without a previous prednisolone response responded to cyclophosphamide. Several authors consider that the maximum cyclophosphamide response is delayed compared with that which occurs with prednisolone.[258 259 263] Side effects are common, occurring in at least one third of patients and requiring discontinuation in most.[252 260 265] The dominant side effects are haematological, haemorrhagic cystitis, and opportunistic infection.[252 266] Doses and regimens used are shown in table 10.

Table 10 Dose regimens for cyclophosphamide and azathioprine

Author	*Regimen used*
Cyclophosphamide	
Johnson[252]	>70 kg, 120 mg/day; 60–69 kg, 110 mg/day; <60 kg, 100 mg/day
Van Oortegem[265]	100 mg/day
Azathioprine	
Meier-Sydow[269]	3 mg/kg/day for 12 weeks, then 2 mg/kg
Raghu[251]	3 mg/kg/day, max 200 mg
Lynch[266]	1–3 mg/kg/day; 50–100 mg initially increasing by 25–50 mg every 2–4 weeks to max 250 mg. Total WBC to stay >3000, WBC monitored every 2 weeks for 4–6 weeks in first instance

Cyclophosphamide and CFA: conclusions

- The efficacy of cyclophosphamide alone is not known.
- Only one controlled trial using cyclophosphamide has been performed. This showed no clear benefit from the addition of cyclophosphamide to low dose prednisolone compared with high dose prednisolone.
- Side effects are common.
- If a response occurs with cyclophosphamide it is thought that this may take several months to become evident.

Azathioprine

No study has looked at azathioprine as a single treatment for CFA compared with placebo or any other treatment. One controlled trial compared high dose prednisolone with high dose prednisolone and azathioprine.[251] There was a non-significant trend to improvement in lung function with the azathioprine regimen and, when adjusted for age, a statistically significant improvement in long term survival (57% versus 23% at nine years). A further prospective study is often cited as evaluating azathioprine in CFA[267] but the patients in this study are heterogeneous, many having features of diseases other than CFA. There are few other reports of the use of azathioprine; two of five patients responded or stabilised in one study,[268] both of two patients responded in another,[147] and six of 11 responded to prednisolone and azathioprine at two years.[269] Two of three patients reported by Weese[270] probably had CFA and stabilised on azathioprine after failing on prednisolone.

The side effects of azathioprine have only been reported in one study, the controlled trial mentioned above.[251] Side effects were reported to be similar in the two groups with a comment that azathioprine was well tolerated. Doses and regimens are given in table 10.

Azathioprine and CFA: conclusions

- As with cyclophosphamide, the efficacy of the drug taken alone is not known.
- A controlled trial showed a survival benefit of azathioprine when added to prednisolone. Side effects were not a problem.

OTHER TREATMENTS

Colchicine

In a retrospective study of 23 patients, 18 of whom had previously been treated with prednisolone, colchicine in a dose of 0.6 mg daily led to improvement in 22% of patients and 39% were stable over 22 months. Two patients discontinued because of gastro-

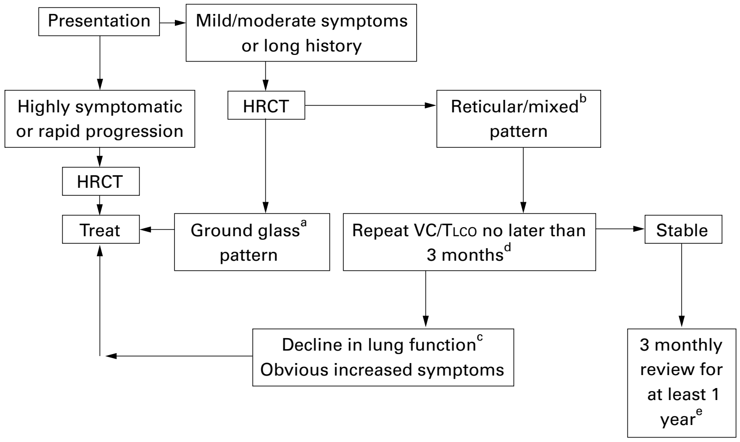


Figure 2 Algorithm of when to treat CFA.[a] "Ground glass pattern" should be predominant, or ground glass only.[b] A mixed pattern of ground glass and reticular shadowing on HRCT scanning is referred to as "mixed".[c] "Decline" in lung function = a sustained fall in VC/TLCO of 10–15% or more.[d] Treatment may be indicated when there is marked impairment in lung function and patient preference is for treatment. (C)[e] After 1 year indefinite follow up is strongly recommended. (C)

intestinal effects.[271] In a further study 22 patients receiving colchicine alone were compared with 22 historical "controls" with UIP given prednisolone. There was no significant difference in the clinical course of these two groups using colchicine 0.6 mg once or twice daily.[272] A recently reported randomised prospective trial of colchicine versus high dose prednisolone found that few patients appeared to respond to either drug, and there were no differences in survival between the two groups.[273]

Penicillamine

Few data are available. In one study three of 10 patients improved at two years on prednisolone and penicillamine[269] and in another one of three patients improved.[147]

Cyclosporin

In seven patients who failed to improve on prednisolone an initial response to cyclosporin was reported but was not maintained; all seven patients died within nine months.[274] In a further study five patients improved and one stabilised on cyclosporin and prednisolone after previous deterioration on prednisolone, but only one improved in both symptoms and lung function.[275] A substantial steroid sparing effect was reported in 10 patients awaiting a lung transplant in a further uncontrolled study.[276]

Methotrexate

There are no reports of the use of this drug in CFA.

Other treatments and CFA: conclusions

- Various treatments have been used including penicillamine, cyclosporin A, and colchicine. Of these colchicine has been best studied, and appears to have a similar effect to prednisolone on the course of CFA, but with fewer side effects. However, as noted previously, it is not known whether prednisolone itself alters the course of CFA.

BTS RECOMMENDATIONS

When to start treatment?

With the uncertain benefits of treatment in CFA, it is essential that treatment is tailored to individual patients. Discussion with patients of the possible outcomes of treatment and side effects is strongly advised. Due account should be taken of comorbidities. In certain patients it will be appropriate not to treat with steroids/immunosuppressants in the light of, for example, the patient's wishes, severe comorbidities, or knowledge of long term disease stability. It is recommended that clinicians otherwise determine when to start treatment using the algorithm shown in fig 2. The recommendations are graded A–C as defined in Appendix 2.

Further points

- Instead of review at three months (fig 2, point *d*), treatment may be indicated when there is a marked reduction in lung function and patient preference is for treatment. (C)
- After one year (fig 2, point *e*) indefinite follow up is strongly recommended. The follow up interval can be extended. Open appointments should be available for patients who deteriorate symptomatically between routine assessments. (C)
- A ground glass predominant pattern indicates underlying pathology that has a potential for spontaneous improvement. This occurs in a minority of cases, however, and treatment is therefore recommended. (B)
- VC/TLCO should be performed where possible at each visit. (B)
- Repeat chest radiography should be performed with unexpected worsening of symptoms or new symptoms such as haemoptysis. (C)

Drug treatment of CFA

- Recommended initial treatment is combined therapy with:
  oral prednisolone 0.5 mg/kg and azathioprine 2–3 mg/kg. (B)
- Patients should be re-assessed at one month. A response or stability should be followed by a slow tail of prednisolone. A decline should be followed by a fast tail (where response or decline = increase or fall in VC/TLCO of 10–15% or more, respectively).
- A response to prednisolone may be seen at one month, but a longer period (up to three months) may be required to assess whether prednisolone has led to stability. (C)
- If there is a response to prednisolone but troublesome side effects, or there are difficulties using steroids at the outset, azathioprine alone should be considered. (C)
- If azathioprine is not tolerated cyclophosphamide should be considered in a dose of 1–2 mg /kg. (C)
- Slow tail of prednisolone: a suggested regimen to tail from 40 mg is a reduction in the daily dose by 5 mg each week to 20 mg. (C) If at review a response or stability is maintained, prednisolone should be further tailed by 5 mg each month to a maintenance dose of 10 mg daily for one year (C) with review at least three monthly with VC/TLCO.

(B) A further slow reduction may be considered subsequently. (C)

- Fast tail of prednisolone: a suggested regimen is a reduction in the daily dose by 10 mg each week to 10 mg daily. (C) Further reduction must be on an individual basis. (C)
- Other treatments should be considered if steroids and immunosuppressants are not tolerated. (C) If these treatments have been tolerated but have failed, the likelihood of a beneficial response to other treatments is very low. Colchicine is an alternative to prednisolone alone (A) but has not been compared with steroid/immunosuppressant combinations.
- In ground glass predominant pattern oral prednisolone alone (without immunosuppressants) is recommended as first line treatment in the regimen described above. (B) In severely ill patients intravenous methylprednisolone should be considered. (C)
- Referral for consideration of transplantation should be considered at an early stage following a failed trial of first line treatment (see page S22). (C)

Fibrosing alveolitis in systemic sclerosis

Fibrosing alveolitis occurring in systemic sclerosis (FASSc) is histologically indistinguishable from that seen in CFA.[277] Nevertheless, FASSc appears to have a better prognosis than CFA,[278 279] even after allowing for age, smoking, and lung function at presentation.[278] Furthermore, several studies have noted wide variability in progression of the disease.[280–282] In some studies 20–50% of patients had spontaneously improved indices of lung function though it is not clear whether these data relate to patients with FASSc.[281 283] Mean TLCO and VC may remain stable without treatment even in the presence of "active" BAL.[149 284] This slower rate of progression in some patients with systemic sclerosis in comparison with CFA must be borne in mind in interpreting treatment studies, especially as there are no randomised controlled trials of treatment in FASSc (though such trials have been carried out in systemic sclerosis in general).

CORTICOSTEROIDS

Surprisingly few studies have assessed the role of steroids. While a case report noted improvement on an unspecified dose of steroids without effect on TLCO,[285] in the study by Tukiainen *et al*[24] eight of 100 patients with fibrosing alveolitis had FASSc and none responded to steroids, though no data are given. In a retrospective analysis of five different treatment modalities high dose steroids were given to 21 patients.[286] Mean FVC declined over 4–6 years though a large variation was noted in individual responses with a "few patients" having a "striking" improvement. This study is analysed in greater detail below. Finally, in a carefully studied group of 79 patients 41 decided not to be treated after discussion. The remainder were given high dose prednisolone initially and cyclophosphamide was added later if there was no response. Unfortunately no comparison is presented on the effects of steroids alone versus no treatment. Overall, the treated group had signficantly better VC and TLCO, whether or not BAL was "active", but the difference was most marked in the "active" group.[149] One study reported an association between high dose steroids and renal crisis in systemic sclerosis.[287]

CYCLOPHOSPHAMIDE

Several studies have evaluated cyclophosphamide in combination with prednisolone either at a low dose,[149 288] high dose,[289] or variable dose.[286] Significant improvements were seen in mean FVC but not in TLCO at 1–2 years[288 289] with 12 out of 14 patients and 14 out of 18 improving or stabilising, respectively. In the retrospective comparison in the different modalities referred to above,[286] patients treated with cyclophosphamide were the only group to increase their mean FVC although there was no improvement in symptoms or survival. Unfortunately, this study is non-randomised and there was substantial variation in the starting VC between groups; furthermore, the cyclophosphamide was given with a variable dose of prednisolone and the drugs were not always given for lung disease. Behr *et al*[149] added cyclophosphamide to patients deteriorating on prednisolone while maintaining a low dose of the latter. There was a statistically significant decrease in decline in VC, but overall the benefits were marginal and do not appear to justify their conclusion that cyclophosphamide should be used at the outset in severe disease.

D-PENICILLAMINE

There was a modest improvement in TLCO in 44 patients treated with D-penicillamine compared with 48 untreated patients but the comparison was retrospective and is therefore difficult to interpret.[284] De Clerck *et al*[290] found no difference between a group treated with D-penicillamine and a group on low dose prednisolone or untreated, though TLCO declined in slightly fewer of the D-penicillamine treated group. VC was not significantly improved in several studies.[284 286 290]

OTHER TREATMENTS

Chlorambucil had no effect on lung function either in a randomised control trial in systemic sclerosis[291] or in an uncontrolled trial in patients with FASSc.[281] In another randomised controlled trial, 5-fluorouracil was also ineffective on an index of lung involvement over six months.[292] Griseofulvin[293] and azathioprine or methotrexate[286] again have not been found to be beneficial in uncontrolled trials. Improvements in lung function were documented in a study in patients receiving multiple immunosuppressants and plasmaphoresis[294] but the study is uninterpretable due to the uncontrolled variety of drugs and lack of comparison data.

Treatment of FASSc: conclusions

- There is evidence that some patients will respond to steroids alone or to cyclophos-

phamide with low dose prednisolone. However, much caution is needed given the lack of controlled trials and the variable course of FASSc. Furthermore, high dose steroids may be associated with renal crisis.
- There is little evidence that D-penicillamine or azathioprine are of benefit, though the latter has received scant attention.

BTS RECOMMENDATIONS
- For FASSc it is reasonable to adopt a similar management plan as for CFA, but using cyclophosphamide as the immunosuppressant in combination with low dose prednisolone as first line therapy. (B)
- Management decisions must take into account the better prognosis of systemic sclerosis and the often slower rate of decline of lung function in this disease. (C)

DPLD in rheumatoid arthritis (RA)

There are no controlled trials of any treatment in DPLD associated with RA. In two of the larger studies of fibrosing alveolitis (FA) 10–19% of patients had co-existing RA and survival was not different in these patients.[23 24] The clinical course of FA/RA appears to be similar.[295 296] Long term stability or spontaneous remission is uncommon.[295] Although progression occurred in under a third of patients in one study, the length of follow up was not given.[297] Progession has been less well studied than for scleroderma, however, but the difficulties of predicting progression in individual patients are highlighted.[295] Further difficulties arise because a wide variety of conditions can present as DPLD in RA, including FA, rheumatoid nodules, COP, and lymphoid interstitial pneumonia,[296] and because some patients will already be on disease modifying drugs such as prednisolone or methotrexate.

CORTICOSTEROIDS

The only study of steroids in FA/RA found that 43% of patients improved exercise tolerance, but there were no remissions of the disease.[298] COP occurring in RA is highly likely to respond to steroids (summarised by Anaya *et al*[296]).

IMMUNOSUPPRESSANTS

Only case reports exist as to the use of immunosuppressants in FA/RA. Intramuscular methotrexate improved symptoms but not lung function in two patients[299] while azathioprine added to prednisolone led to improvement in another.[300] Cyclosporin and prednisolone benefited one patient[301] but not another.[295]

Treatment of FA/RA: conclusions
- The extreme paucity of data means that evidence based treatment is not available in FA/RA.

BTS RECOMMENDATIONS
- The management of FA/RA should follow the same lines as for CFA. (C)
- COP in rheumatoid arthritis is likely to respond to steroids. (B)

Pulmonary sarcoidosis

CORTICOSTEROIDS

The beneficial effects of corticosteroids in pulmonary sarcoidosis were first reported in 1951[302] and they have been widely used since the 1960s. Both uncontrolled[303 304] and controlled studies,[305–309] as well as common clinical experience, have amply demonstrated short to medium term (weeks to months) symptomatic, radiographic, and functional improvement. Even in patients with chronic disease untreated for several years, the introduction of steroids may produce readily apparent benefit.[310]

The long term (years) outcome of steroid treatment is more uncertain with most studies showing no evidence of benefit (table 11). However, assessment is complicated by differences in the pattern of disease and the natural history; in most patients this is towards spontaneous regression, albeit often with a variable degree of residual scarring. Estimates of significant long term disability due to pulmonary fibrosis vary from 3% to 20% of patients.[315] Most controlled studies of long term outcome can be criticised on one or more counts:

(1) Several included patients with bilateral hilar lymphadenopathy (BHL "stage 1") only. Since such patients have an almost universally good prognosis for spontaneous resolution with little or no disability, their inclusion weakens the power of a study to detect a treatment effect.
(2) In most studies steroids were introduced at presentation, even in asymptomatic patients, whereas many clinicians adopt an initial policy in such patients of "wait and see". The importance of delaying treatment was demonstrated in the recent BTS controlled study[76] in which half of the

Table 11 Long term outcome of controlled studies of corticosteroids in pulmonary sarcoidosis

Authors	*Preliminary observation period (+/−)*	*Total no. (pulmonary shadowing)*	*Allocation method*	*Control group*	*Steroid duration (months)*	*Follow up mean (years)*	*Assessment**	*Outcome*
Young *et al*[311]	−	25 (?)	Alternate	No treatment	6–24	1.5	F	No differences
Harkleroad *et al*[312]†	−	17 (10)	Alternate	No treatment	6–24	11	R, F	No differences
Hapke and Meek[305]	−	22 (?)	Alternate, matched pairs	No treatment	6	4	R, F	No differences
Israel *et al*[306]	−	83 (46)	Random	Placebo	3	5.2	S, R, F	No differences
Mikami *et al*[307]	−	101 (35)	Random	Placebo	6	1	R	No differences
Selroos *et al*[308]	−	37 (37)	Random	No treatment	7	4	R, F	No differences
Yamamoto *et al*[313]	−	74 (42)	Retrospectively matched pairs	No treatment	18	3	R	No differences
Eule *et al*[309]	−	172 (105)	Random	No treatment	6 or 12	8.9	R, F	No differences
Zaki *et al*[314]	−	159 (78)	Random matched pairs	Placebo	>24	>3	R, F	No differences
Gibson *et al*[76]	+	58 (58)	Alternate	No treatment	>18	5.1	S, R, F	Higher "clinical score", final VC 9% predicted higher

*F = respiratory function; R = chest radiograph; S = symptoms. †Prolonged follow up of patients in reference 311.

patients not immediately requiring steroids for control of symptoms showed regression of pulmonary shadowing over a six month observation period.

(3) Most North American studies have included a preponderance of black subjects in whom the natural history of sarcoidosis is usually more aggressive; the results may not be generalisable to European patients.

(4) Most studies used a standard treatment regimen rather than individually tailoring the steroid dose in a manner comparable to usual clinical practice.

The BTS study of long term steroid therapy attempted to take account of these criticisms by concentrating on patients in whom spontaneous improvement was not seen after a six month observation period.[76] Patients managed according to a policy of steroid treatment aimed at producing and maintaining maximum radiographic improvement were slightly better after five years of observation than those in whom an expectant policy was continued with steroids introduced only if troublesome symptoms developed.[76] On average, patients in the former group had a significantly better "clinical score" (combining symptoms, chest radiography and lung function) after five years. Of the individual indices, mean predicted VC showed the most significant difference, being 9% greater in the group on long term treatment. The proportions of patients requiring steroids at final assessment in the two groups were 18% and 13%, respectively.[76]

In a simultaneous open study of 33 symptomatic patients requiring early steroid treatment, it was noteworthy that 45% continued to take steroids after five years, usually because of relapse of symptoms when dose reduction or withdrawal was attempted. Such relapses are well recognised[316 317] and, in a recent retrospective study, Gottlieb *et al*[318] showed that relapse was much more common in patients previously treated with corticosteroids than in those in whom spontaneous regression has occurred. They argued that the steroids themselves may contribute to prolongation of the disease by delaying its resolution. However, only a few of the subjects in this study were treated primarily for respiratory symptoms (as opposed to disease affecting other organ systems), the majority were black Americans, and the group who showed spontaneous remission clearly had milder disease at the onset. Thus, while it remains feasible that steroids may have led to more prolonged disease by delaying resolution, this has not been addressed formally in a prospective study. The possibility should be borne in mind when steroid treatment is being considered for patients with only relatively mild symptoms. Experience from both these recent studies[76 318] emphasises the fact that patients who sustain the most severe long term damage due to pulmonary sarcoidosis are nearly always recognisable early in their course, and almost inevitably require steroids for symptomatic relief. It is also clear that, once spontaneous regression has occurred (most frequently in patients with relatively mild disease at presentation), later relapse is distinctly unusual.

The initial daily dose of prednisolone (or equivalent) in controlled studies has varied between 30 mg and 60 mg per day, usually reducing progressively each month, subject to satisfactory response, to an average of 10 mg daily maintained for 6–12 months before attempting gradual withdrawal. Alternate day treatment (equivalent to the same average daily dose) has been proposed as a way of limiting side effects[319] and has been shown in a controlled study[320] to be as effective as daily treatment.

OTHER ANTI-INFLAMMATORY AND IMMUNOSUPPRESSANT AGENTS

Several other drugs have been used in the treatment of pulmonary sarcoidosis, often as steroid sparing agents.[321] These include chloroquine,[322] chlorambucil,[323 324] methotrexate,[325 326] azathioprine,[327] cyclophosphamide,[321] cyclosporin,[328 329] and pentoxifylline.[330] Most reports are of uncontrolled observations in patients with advanced disease and suggest limited activity of the drugs. A controlled study[322] compared chloroquine with placebo for four months as primary treatment of patients with persistent pulmonary shadowing; at the end of this period the chest radiograph had improved significantly more with active drug, with concomitant improvements in symptoms and ventilatory function. After a further eight months, however, the difference had not been sustained. Patients receiving chloroquine require regular visual assessment. Hydroxychloroquine is an alternative which may have fewer gastrointestinal side effects.[321] A regime of cyclosporin at 5–7 mg/kg/day and prednisolone (tapering from 20 mg/day) has recently been shown in a randomised controlled trial to offer no significant benefit over prednisolone alone.[329] In an uncontrolled review of treatment with methotrexate for at least two years in 50 patients with chronic sarcoidosis, one third of those with pulmonary disease improved.[326] All these drugs have potentially serious side effects. Anecdotal evidence suggests that, apart from chloroquine, methotrexate or azathioprine may be the agents of choice.

INHALED CORTICOSTEROIDS

The beneficial effect of inhaled budesonide in pulmonary sarcoidosis was first reported by Selroos in 1986[331] in an open study of 20 patients. Subsequently, several open and controlled studies have investigated the potential value of inhaled steroids, either as primary treatment or as maintenance treatment once oral steroids have induced a response (table 12). One open study of beclomethasone dipropionate reported in a large group of Indian patients[332] showed uncertain benefit. The other studies have all been of budesonide. Zych *et al*[333] reported a double blind, double dummy comparison of oral prednisolone and inhaled budesonide as maintenance treatment after initial treatment with prednisolone. After 12 months' treatment the two groups were similar but, in the absence of a placebo or untreated maintenance group, the study was not conclusive. Selroos *et al*[334] in an open study of maintenance treatment showed progressive improve-

Table 12 Controlled studies of inhaled budesonide in pulmonary sarcoidosis

Authors	*Initial (I) or maintenance (M)*	*Dose (mg/day)*	*Total no. (pulmonary shadowing)*	*Allocation method*	*Control group*	*Duration (months)*	*Follow up (months)*	*Assessment**	*Outcome*
Zych *et al*[333]	M	1.6	40 (40)	Random	Prednisolone 10 mg/day	12	12	R, F	No differences
Milman *et al*[335]	I	1.2–2.0	21 (?)	Random	Placebo	12	18	S, R, F	No differences
Alberts *et al*[336]	I	1.2	47 (34)	Random	Placebo	6	12	S, R, F	Higher VC and fewer symptoms with active treatment

*F = respiratory function; R = chest radiograph; S = symptoms.

ment in the chest radiograph and pulmonary function. Although the study was not controlled, patients were treated only after a period of at least six months, during which they failed to show spontaneous recovery. The results are suggestive of benefit but seven patients subsequently required oral steroids after failing to respond to increased doses of budesonide.

In a small randomised, double blind, parallel group study of 21 patients in which budesonide was compared with placebo as initial therapy, Milman *et al*[335] showed no differences at 12 months and similar numbers of patients in the two groups required oral steroids during that period. The treatment was introduced without a preliminary observation period. In the largest placebo controlled study published to date, Alberts *et al*[336] evaluated budesonide as initial treatment without a preliminary observation period and having excluded an unstated number of patients with severe symptoms. After six months' treatment the active group showed significantly better VC and symptoms but no differences in TLCO or in the chest radiograph. Four of 22 in the budesonide group and seven of 25 in the placebo group required the introduction of oral steroids during this period.

In conclusion, therefore, inhaled budesonide is less reliable than prednisolone as primary treatment for patients with pulmonary sarcoidosis. It may have a role as maintenance treatment as an adjunct to, or substitute for, oral steroids in some patients but no specific criteria are available to identify patients who are likely to respond. Although theoretically appealing, there is no evidence that early treatment of pulmonary sarcoidosis with inhaled steroids affects outcome.

TRANSPLANTATION

Transplantation is reviewed on page S23.

BTS RECOMMENDATIONS

- Most patients who present with pulmonary sarcoidoisis do not need treatment. (B)
- Treatment with steroids is rarely necessary in patients with BHL alone and no pulmonary shadowing ("stage 1") (B) but troublesome cough or concomitant non-respiratory symptoms such as troublesome arthropathy or lethargy occasionally justify their use. (C)
- In patients with pulmonary shadowing and no (or trivial) symptoms treatment should not be initiated immediately but the patient should be monitored for at least six months. A large proportion of such patients will show radiographic improvement over this period. A smaller proportion will become symptomatic and should receive treatment as outlined below. (B)
- Treatment is recommended for the control of persistent symptoms, most commonly shortness of breath and sometimes cough. In patients with persistent chest radiographic shadowing after six months of observation, steroid treatment should be considered but the average long term benefit is small and subsequent withdrawal of treatment may be difficult. (A)
- Oral steroids using prednisolone 0.5 mg/kg daily (or equivalent) are the treatment of choice. (B) The maximum dose should normally be maintained for at least four weeks and, subject to satisfactory response, should then be reduced stepwise to a maintenance dose which is adequate to maintain control of symptoms. Usually this is 5–15 mg daily. This dose should be continued for several months before further reduction, which should be gradual (by no more than 2.5 mg/day per month to 5 mg/day and by no more than 1 mg/day per month thereafter). (C)
- In most cases the effect of treatment is appropriately monitored by the combination of symptoms, chest radiography, and lung function (VC/TLCO). (B)
- Relapse following reduction or withdrawal of steroids is not uncommon and may necessitate an increased dose or reintroduction of steroids. Steroid withdawal symptoms may, however, sometimes be difficult to differentiate from disease relapse. A decision to increase or reintroduce steroids should therefore be taken with care and be based primarily on those indices of disease activity that led to steroids being introduced. (C)
- Inhaled steroids are not indicated as initial treatment of symptomatic patients. (A) Budesonide may have a role as maintenance treatment once disease activity has been suppressed by oral steroids and its use should be considered in patients with only mild symptoms, or as an adjunct to oral maintenance therapy in those requiring large doses. (C)
- Other anti-inflammatory agents have a limited role in pulmonary sarcoidosis (although they may have stronger indications in non-pulmonary disease such as in disfiguring skin lesions). They should be considered in patients in whom side effects of steroids are intolerable. All are potentially toxic and their use requires careful monitoring. (B) Chloroquine or methotrexate should be considered in the first instance. (B)

Brief notes on treatment of some rarer DPLDs

EXTRINSIC ALLERGIC ALVEOLITIS

Initial treatment should be removal of the patient from further exposure to the antigen. This alone may lead to rapid resolution of the disease. In acute episodes with persisting symptoms, oral corticosteroids should be introduced (0.5 mg/kg per day) until symptoms and radiographic changes have resolved. Corticosteroids accelerate the recovery period but do not alter the ultimate level of lung function.[338 339] Continued exposure to the antigen is not necessarily associated with progressive deterioration in lung function.[340] Symptomatic recurrences may be important in determining those who progress.

CRYPTOGENIC ORGANISING PNEUMONIA

Organising pneumonia is often secondary to a variety of underlying causes which will be important in determining the outcome. Cryptogenic cases respond well to corticosteroids in two thirds or more of patients.[10 341] Steroids are usually started at about 40 mg daily and reduced to zero over 6–12 months.[342] Some patients relapse and require repeated courses of steroids. A few have a rapidly progressive course with fatal outcome despite steroids.[343]

ALVEOLAR PROTEINOSIS

Since spontaneous remission occurs in approximately one third of patients, treatment should only be instituted for deteriorating symptoms and/or lung function. Corticosteroids should probably not be used, given the increased risk of fungal infection in the disease.[344 345] The treatment of choice is whole lung lavage. The prognosis using this therapeutic intervention is good, with 25–50% of patients achieving permanent remission after a single lavage and the remainder requiring repeated lavages at regular intervals.[127 346] Death is now rare.

PULMONARY LANGERHANS' CELL HISTIOCYTOSIS

Cigarette smoking is strongly associated with the development of pulmonary LCH. Initial treatment should be to encourage smoking cessation. This may result in stabilisation or resolution of LCH.[347] In patients with severe symptoms or deteriorating lung function and/or radiology, a trial of steroids should be given. In patients with progressive disease a radiological response of 85% has been reported but with improvements in lung function only in VC.[348] In those non-responsive to steroids, cytotoxic drugs may be considered. In disseminated disease cytotoxic drugs (etoposide or vinblastine) are frequently used[349 350] but there are no studies addressing the effects of cytotoxic treatment on pulmonary disease. An alternative approach is immunomodulation using agents such as cyclosporin A.[351] The prognosis with isolated lung involvement is variable; 25% spontaneously remit, 50% stabilise, and 25% progress.[78]

LYMPHANGIOLEIOMYOMATOSIS (LAM)

This rare disease is confined to women of childbearing age and treatment has therefore been directed at hormonal manipulation. Its rarity precludes controlled trials and treatments have included oophorectomy, ovarian irradiation, progesterone, and tamoxifen.[79] It has recently been suggested that all asymptomatic patients with LAM should receive at least a one year trial of 400–800 mg intramuscular medroxyprogesterone per month.[80] Oral medroxyprogesterone may also be given at 10–20 mg daily.[352]

PULMONARY CAPILLARITIS AND ALVEOLAR HAEMORRHAGE

Identification of the underlying disease is of fundamental importance in determining treatment. Therapy usually includes prednisolone and cyclophosphamide or azathioprine.[353]

Referral for lung transplantation

LUNG TRANSPLANTATION IN CFA

Of patients with DPLD, those with CFA are the largest group referred for transplantation.

When should patients be referred?

Current therapy for CFA has limited success (see page S15–18) and patients commonly develop life threatening disease despite optimal medical treatment. Such patients may be offered single lung transplantation which, for CFA, results in an actuarial survival of 80% at one year and 55% at three years.[354]

The timing of referral for transplantation is dependent on predicting survival. Traditionally, a median survival of five years following the diagnosis of CFA is quoted.[23 24 100] Such data probably reflect referral patterns to tertiary centres, with possible selection bias against those with rapidly progressive disease. Recent data confirm that newly diagnosed patients (incident cases) have a median survival of only 2.9 years (34 months).[355] These epidemiological data mirror estimates of survival based on histological subcategories which show a survival of 2.8 years for patients with UIP (the commonest histological pattern in CFA).[255]

Currently, the median waiting period for single lung transplantation in the UK is 351 days (CI 293 to 427 days).[356] A limited window of opportunity (22 months) therefore exists to refer patients for potential lung transplantation (34 months survival minus 12 months waiting = transplant window of 22 months). The short transplant window is reflected in the high mortality rate in patients with CFA awaiting lung transplantation.[354] To correct for this limited transplant window patients with CFA in the USA are given a three month waiting advantage compared with patients with emphysema.[357]

It is current practice to monitor lung function and refer patients receiving corticosteroid and/or immunosuppressant therapy for transplantation when patients are highly symptomatic and in need of oxygen therapy. In end stage CFA, however, lung function may be a poor marker of survival.[264]

It is therefore recommended (C) that symptomatic patients with CFA under the age of 65 (see below) should be discussed with the transplant centre following a failed trial of corticosteroid therapy and referred in any of the following circumstances[358]:

- TLCO and/or VC below 50–60%;
- resting hypoxia;
- pulmonary hypertension.

Which patients should be referred?

Age is a limiting factor for solid organ transplantation. The usual upper limit of 60 years excludes most patients with CFA as it is a disease of the elderly.[2 8] Providing they are physically robust, patients up to 65 years should be discussed with the transplant centre.

If a patient is a potential candidate for transplantation, the minimum criteria include (C):

- Normal left ventricular function assessed by echocardiography and electrocardiography.
- Creatinine clearance >50 ml/min.
- A recent HRCT scan: an atypical HRCT scan may suggest the need for a tissue biopsy sample, particularly to exclude malignancy.
- An atypical clinical course may also suggest the need for a tissue biopsy sample to be taken to exclude malignancy.
- Hepatitis B and C seronegative.
- HIV seronegative.
- The absence of a recent history of malignancy (>5 years).
- The absence of severely symptomatic osteoporosis (T score less than –2).
- Smoking cessation for >6 months.

LUNG TRANSPLANTATION IN OTHER DPLDS

Lung fibrosis associated with systemic disease

Pulmonary fibrosis complicates many systemic diseases (see table 5). Such patients remain potential candidates for transplantation but each patient must be evaluated individually. General criteria of acceptance include (C):

- current evidence of quiescent systemic disease;
- creatinine clearance of >50 ml with no evidence of renal vasculitis;
- the absence of severe gastro-oesophageal reflux resulting in aspiration;
- other criteria as for CFA (see above).

Sarcoidosis

In end stage pulmonary fibrosis the primary disease may be difficult to identify. Sarcoidosis may mimic CFA and a diagnosis may only be made after histological examination of the explanted lung.[359] Although sarcoidosis can recur following lung transplantation,[337] patients may still be considered for the procedure since there is no evidence that recurrent sarcoidosis following transplantation results in a higher rate of graft failure than the more common post transplant complication of obliterative bronchiolitis.[337] Criteria for acceptance include (C):

- exclusion of active infection with *Aspergillus fumigatus* in apical cavities;
- careful evaluation of cardiac function, ideally undertaken with MRI;
- other criteria as for CFA (see above).

LCH and LAM

The pre-transplant survival of patients with LCH and LAM is similar to patients with emphysema, and is therefore significantly better than for patients with CFA.[360]

In LCH and LAM, consideration for transplantation is indicated in the event of severe disability (FEV_1 <30% of predicted) and oxygen dependency. (C)

PNEUMOTHORAX IN PATIENTS AWAITING LUNG TRANSPLANTATION

Spontaneous pneumothorax is a recognised complication of LCH and LAM and can be a pre-terminal event in patients with CFA. The priority of treatment must be to preserve survival and minimise loss of functional lung capacity. If a pneumothorax is refractory to standard medical management, surgical intervention with chemical or mechanical pleurodesis is appropriate if technically possible. Pleurodesis may result in the explantation of the lung at the time of transplantation being technically more difficult, but in itself is not a contraindication to transplantation. (C)

LIAISON WITH TRANSPLANT CENTRE

These recommendations are not prescriptive. Should doubt remain as to whether a patient is a suitable candidate or not, discussion with the transplant centre is welcomed prior to discussion with the patient. Repeated and detailed communication between the referring physician and transplant centre is a vital component of the selection and continuing monitoring of the patient prior to transplantation. (C)

General considerations in the treatment of DPLDs

IMMUNOSUPPRESSANTS

Clinicians using such drugs must be aware of the many potential side effects.[266] Haematological and liver function monitoring according to nationally or locally agreed guidelines is essential. In patients receiving cyclophosphamide, monitoring for haematuria is mandatory.

OSTEOPOROSIS

All patients starting treatment with corticosteroids should be assessed as to their risk of developing osteoporosis.[361] The use of bisphosphonates limits the severity of steroid-induced osteoporosis.[362–364] Again it is appropriate to follow national or locally agreed policies. In general, calcium and vitamin D therapy is not recommended in sarcoidosis.

COR PULMONALE

In patients with severe DPLD treatment of cor pulmonale is frequently needed. In CFA, in particular, co-morbidities such as heart failure are frequently present and should be actively sought and treated. Patients with severe DPLD should be assessed for oxygen therapy.

Appendix 1: Reviewers participating in the BTS recommendations on the diagnosis and assessment of DPLD

BTS Standards of Care Committee
Dr M Muers (Chairman), Consultant Physician
Dr I I Coutts, Consultant Physician
Dr H W Clague, Consultant Physician
Dr W J M Kinnear, Consultant Physician
Dr T J Williams, Consultant Physician
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Further reviewers
Mr P Goldstraw, Consultant Thoracic Surgeon
Ms D C T Watson, Consultant Thoracic Surgeon
Professor A Casson, Professor of Thoracic Surgery
Professor B Corrin, Professor of Thoracic Pathology
Dr A R Gibbs, Consultant Pathologist
Dr W A H Wallace, Consultant Pathologist
Dr D M Hansell, Consultant Radiologist
Dr F Gleeson, Consultant Radiologist
Dr M D L Morgan, Consultant Physician
Dr A J Peacock, Consultant Physician
Dr I C Paterson, Consultant Physician
Dr A Woodcock, Consultant Physician
Dr W F Holmes, General Practitioner

Appendix 2: Grading scheme for recommendations

The criteria for the grading of recommendations are based on a paper by Petrie *et al* published on behalf of the Scottish Intercollegiate Guidelines Network.[365]

Table 13 Levels of evidence

Level	*Type of evidence (based on AHCPR 1992*[366]*)*
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well designed quasi-experimental study
III	Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies and case controlled studies
IV	Evidence obtained from expert committee reports of opinions and/or clinical experience of respected authorities

Table 14 Grading of recommendations

Grade	*Type of recommendations (based on AHCPR 1992*[366]*)*
A (levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation
C (level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

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